

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

UNITED THERAPEUTICS CORP.,

Plaintiff,

v.

SANDOZ, INC.,

Defendant.

Civil Action Nos. 12-CV-01617

13-CV-316

MEMORANDUM

Sheridan, U.S. District Judge

Pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j), this consolidated patent infringement action is brought by Plaintiff, United Therapeutics Corporation (“Plaintiff” or “UTC”), against Defendant, Sandoz, Inc. (“Defendant” or “Sandoz”), for infringement of United States Patent Nos. 6,765,117 (“the ’117 patent”) and 7,999,007 (“the ’007 patent”)(collectively the “patents-in-suit”)¹—which Plaintiff has listed in the Orange Book in connection with treprostinil sodium injection. On March 14, 2012, UTC filed the first of two lawsuits against Sandoz for patent infringement based upon Sandoz’s submission of ANDA No. 203649 to the FDA, seeking approval to market and sell a generic form of UTC’s patented treprostinil sodium injection. *See United Therapeutics Corporation. v. Sandoz, Inc., et al.*, Civil No. 12-1617.² On January 16, 2013, UTC filed a second suit against Sandoz for patent infringement, based upon Sandoz’s subsequent amendments to ANDA No. 203649. *See United Therapeutics Corporation. v. Sandoz, Inc., et al.*,

¹ Plaintiff’s complaints also included allegations that Sandoz would infringe a third patent listed in the Food and Drug Administration’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (commonly referred to as the “Orange Book”) in connection with REMODULIN, U.S. Patent No. 5,153,222 (“the ’222 Patent”). On April 9, 2014, Sandoz converted its paragraph IV certification regarding the ’222 patent to a paragraph III certification. On June 2, 2014, in accordance with that decision, the Court dismissed the counts in UTC’s Complaints alleging infringement of the ’222 patent without prejudice, along with Sandoz’s counterclaims for non-infringement and invalidity of the ’222 patent. (ECF No. 336).

² For purposes of this decision, references to the docket will pertain to the first case filed, 12-1617, unless otherwise

13-316 (“13-316”). By agreement of the parties, this consolidated action followed.³

The Court held a *Markman* hearing on May 20, 2013, and on June 25, 2013, the Court issued an Order construing disputed terms. (ECF No. 95). The Court conducted a 14-day bench trial from May 2-May 29, 2014. (ECF Nos. 345-358). The parties completed post-trial briefing on June 20, 2014, and in connection with same, the parties submitted proposed findings of fact and conclusions of law. ECF Nos. 343, 360, 341, 342. Presently before the Court are the parties’ post-trial proposed findings of fact and conclusions of law concerning the infringement and validity of the patents-in-suit.

Pursuant to *Federal Rule of Civil Procedure 52(a)*, and after careful consideration of the entire record in this case and the applicable law, the Court hereby concludes that: (1) UTC has failed to prove by a preponderance of the evidence that Sandoz’s proposed ANDA product will induce infringement of the asserted claims of the ‘007 patent; (2) Sandoz has failed to prove by clear and convincing evidence that the asserted claims of the ‘007 are invalid; (3) UTC has proved by a preponderance of the evidence that Sandoz’s ANDA product will infringe and induce infringement of the asserted claims of the ‘117 patent; and (4) Sandoz has failed to prove by clear and convincing evidence that the asserted claims of the ‘117 patent are invalid.

The Court's findings of fact and conclusions of law are set forth in detail below.

I. Background

A. Parties

Plaintiff United Therapeutics Corporation (“United Therapeutics” or “UTC”) is a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 1040 Spring Street, Silver Spring, Maryland 20910.

Defendant Sandoz Inc. (“Sandoz”) is a corporation organized and existing under the laws

noted.

³ On May 14, 2013, the parties filed a joint stipulation that the parties’ briefs associated with XYZ Corporation’s Motion to Dismiss UTC’s Complaint in Civil Action No. 13-316 would be deemed filed in Civil Action No. 12-1617. (ECF 86.) On June 3, 2013, the Court issued a pretrial scheduling order where it found good cause to keep both Civil Action No. 12-1617 and Civil Action No. 13-316 cases on the same schedule where feasible to avoid duplicate discovery. (ECF 91.) On July 1, 2013, the parties filed a joint stipulation that the parties’ briefs associated with Defendants’ Motion for Leave to Supplement its Invalidity Contentions for U.S. Patent No. 6,765,117 in Civil Action No. 12-1617 would be deemed filed in Civil Action No. 13-316. (13-316, ECF 35.)

of the State of Colorado, having a principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

B. Remodulin

United Therapeutics holds an approved New Drug Application (No. 21-272) (“NDA”) for Treprostinil Sodium Injection, marketed and sold under the federally registered trademark REMODULIN^{®4} for the treatment of pulmonary arterial hypertension. Pulmonary arterial hypertension (or “PAH”) is a rare, debilitating, and potentially fatal disease, in which the blood pressure between the heart and lungs rises to dangerously high levels, narrowing the arteries and depriving the body of oxygen.⁵

Remodulin is an injectable product indicated for the treatment of pulmonary arterial hypertension. It was first approved in the United States in May 2002, and is presently approved for sale in concentrations including 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL.

C. U.S. Patent No. 6,765,117 Background

Stereochemistry is the study of the relative spatial arrangement of atoms that form the structure of molecules. The stereochemistry of any given compound is an integral and highly significant aspect of its physical and functional properties.

When a carbon atom of a molecule is bonded to four different groups, that carbon atom is said to be “chiral” or constituting a “chiral center.” A chiral center is also commonly called a “stereogenic center.” Each chiral center in a molecule results in two possible stereoisomers. Stereoisomers have the same molecular formula, sequence of atoms, and connectivity of atoms and differ only with respect to the three-dimensional spatial arrangement of their atoms within the molecule.

⁴ Hereafter “Remodulin”

⁵ The Court has previously construed “pulmonary hypertension” to mean “increased resistance to pulmonary blood flow resulting in greater pressure in the circulation for any particular flow, which is generally defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities, and which includes both primary and secondary pulmonary hypertension as ordinarily understood by clinicians.” *Markman* Order, June 25, 2013 (ECF 95 at 10, 25.)

It “is extremely important to the proper biological function” of a drug to obtain the specific stereoisomer of a compound, because typically, only one stereoisomer behaves in a desirable manner (Tr. 48:8-12 (Williams), May 1, 2014); other stereoisomers may have no biological effect or a deleterious biological effect. (Tr. 48:13-17 (Williams), May 1, 2014.)

Treprostinil sodium is the active pharmaceutical ingredient (“API”) of the generic treprostinil injection that is the subject of Sandoz’s ANDA. Treprostinil is one of a class of biochemicals that are derived from naturally occurring hormonal substances found in human and animal tissues, called prostacyclin derivatives. The prostacyclin derivative that gives rise to treprostinil is a complex compound containing five chiral centers (Tr. 44:18-25 (Williams), May 1, 2014; Tr. 2052:3-5 (Gorin), May 22, 2014); therefore thirty-two stereoisomers of the molecule are possible. A particular stereoisomer of the prostacyclin derivative is able to mimic the function of the natural hormone prostacyclin by bonding to the same biological receptor to which natural prostacyclin bonds, (Tr. 48:1-8 (Williams), May 1, 2014), because it has the same configuration at the five chiral centers as the natural hormone prostacyclin. (Tr. 48:1-8 (Williams), May 1, 2014.) For that reason, this particular stereoisomer, known as “Treprostinil”⁶, is the most efficacious and therefore the most desirable of all thirty-two possible stereoisomers. A stereoselective synthesis will make more of this ideal stereoisomer—“Treprostinil”—than any of the other thirty-two possible stereoisomers. (Tr. 2051:17-2052:1 (Gorin), May 22, 2014.)

On a molecular level, there is no sample of Treprostinil that is 100% pure. (Tr. 45:16-17 (Williams), May 1, 2014; Tr. 1734:14-25, 1723:6-10, 1723:16-20 (Aristoff), May 16, 2014.) Each sample of Treprostinil carries with it characteristic impurities including other stereoisomers and impurities related to the synthetic process. (Tr. 1458:9-14 (Buchwald), May 15, 2014.) A person of ordinary skill in the art at the time of the invention would understand that a stereoselectively produced product is a product consisting primarily of one stereoisomer over any other stereoisomers. (Tr. 52:3-8, 52:14-20 (Williams), May 1, 2014.)

⁶ In the case at bar, the term “treprostinil” is used interchangeably to refer to this specific stereoisomer as well as a mixture of stereoisomers that includes treprostinil.

D. U.S. Patent No. 6,765,117

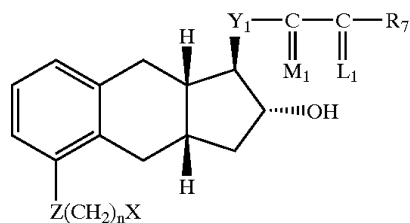
The '117 patent, entitled "Process for stereoselective synthesis of prostacyclin derivatives," was issued by the PTO on July 20, 2004. The '117 patent is scheduled to expire on October 24, 2017. The named inventors on the '117 patent are Robert M. Moriarty, Raju Penmasta, Liang Guo, Mungala S. Rao, and James P. Staszewski. The application that matured into the '117 patent was a division of application no. 09/541,521, filed on April 3, 2000, now U.S. Patent No. 6,441,245, which is a continuation-in-part of application no. 09/481,390, filed on January 12, 2000, which is a continuation of application no. 08/957,736, filed on October 24, 1997. The '117 patent priority date is October 24, 1997. The '117 patent is assigned on its face to United Therapeutics Corporation. United Therapeutics is the owner of the '117 patent by assignment. Example 1 in the '117 patent is an embodiment of the claimed invention of the '117 patent.

1. Asserted Claims

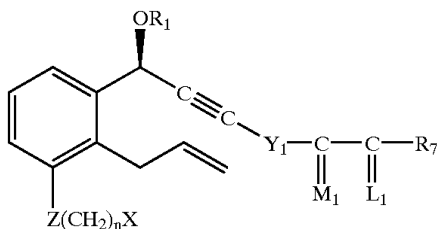
UTC asserts that Sandoz's proposed generic product and/or manufacturing process will infringe claims 1-4 of the '117 patent. (ECF No. 218, Exhibit 1 to Pretrial Order, Stipulated Fact No. 30). The asserted claims are reproduced on the pages that follow:

Claim 1

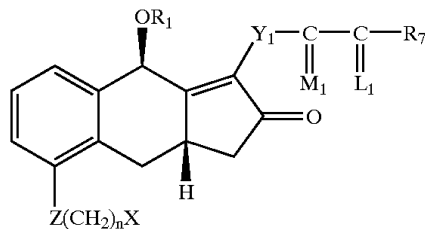
1. A stereoselectively produced isomeric compound according to the following formula:



that is produced by a process for making 9-deoxy-PGF₁-type compounds, the process comprising cyclizing a starting compound of the formula:



into a compound of the following formula:



by intramolecular cyclization of the enyne,
wherein

Z is O, S, CH₂, or NR₈ in which R₈ is H, alkyl or aryl;
X is H, CN, OR₉, or COOR₉ in which R₉ is H, alkyl,
a pharmacologically acceptable cation, THP or
TBDMS;
wherein n is 0, 1, 2, or 3;

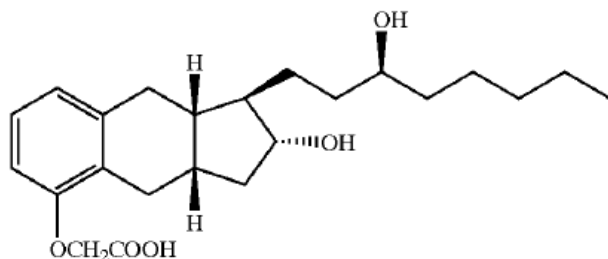
Claim 2

The stereoselectively produced isomeric compound of claim 1, wherein Z is O, n is 1, X is COOH, Y₁ is -CH₂CH₂- M₁ is α-OH:β-R₅, wherein R₅ is hydrogen, L₁ is α-R₃:β-R₄, wherein R₃

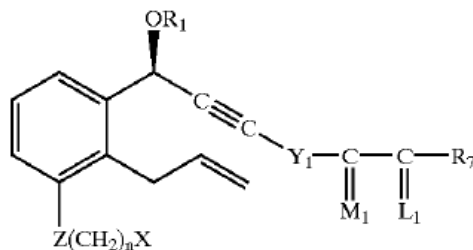
and R_4 are hydrogen and R_7 is butyl.

Claim 3

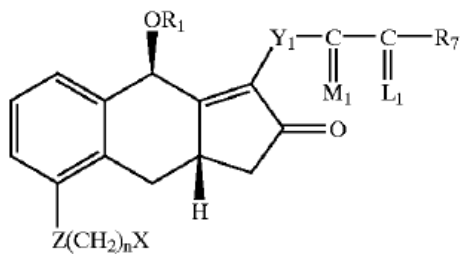
3. A stereoselectively produced isomeric compound according to the following formula:



that is produced by a process for making 9-deoxy-PFG₁-type compounds, the process comprising cyclizing a starting compound of the formula:



into a compound of the following formula:



by intramolecular cyclization of the enyne,
wherein

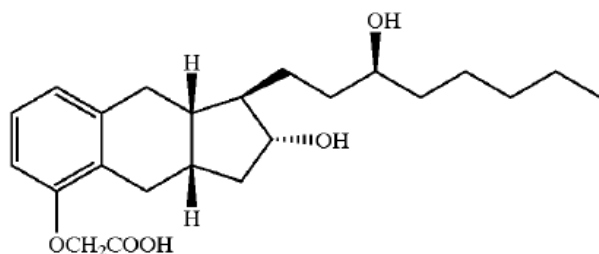
Z is O, S, CH₂, or NR₈ in which R₈ is H, alkyl or aryl;

X is H, CN, OR₉, or COOR₉ in which R₉ is H;

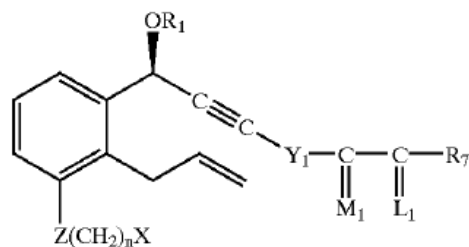
wherein n is 0, 1, 2, or 3;

Claim 4

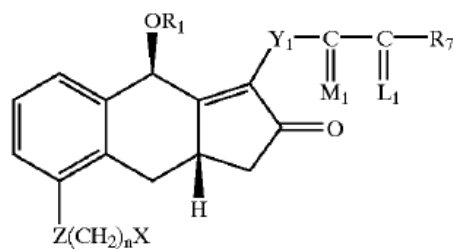
4. A stereoselectively produced isomeric compound in pharmacologically acceptable salt form according to the following formula:



that is produced by process for making 9-deoxy-PGF₁-type compounds, the process comprising cyclizing a starting compound of the formula:



into a compound of the following formula:



by intramolecular cyclization of the enyne,
wherein

Z is O, S, CH₂, or NR₈ in which R₈ is H, alkyl or aryl;

X is H, CN, OR₉, or COOR₉ in which R₉ is a pharmacologically acceptable cation;

wherein n is 0, 1, 2, or 3;

During trial, a belated dispute arose between the parties as to the proper construction of the phrase “stereoselectively produced isomeric compound” as used in ‘117 patent claims 1-4. At that time, the Court permitted the parties to brief the issue (ECF Nos. 322, 323) and heard the parties’ oral arguments as to the proper claim construction. The Court construed the phrase “stereoselectively produced isomeric compound” present in each claim of the ‘117 patent to mean “the product of claims 1 through 4 of the ‘117 patent.” May 22, 2014 Order, ECF No. 328 at 2. The Court also clarified that the plain and ordinary meaning of “stereoselectively produced isomeric” is an adjectival phrase modifying the word “compound.” *Id.*

E. U.S. Patent No. 7,999,007 Background

Not long after patients began using Remodulin subcutaneously, it became apparent to many physicians that some PAH patients simply could not tolerate subcutaneous injections of Remodulin, experiencing severe pain at the injection site. In November 2004, Remodulin was approved by the FDA for intravenous infusion, offering patients a welcome alternative method of administering Remodulin.

When administered subcutaneously, Remodulin is administered without dilution. When administered by intravenous infusion, Remodulin must be diluted prior to injection through an indwelling central venous catheter. In November 2004, the FDA approved a revised package insert or label for Remodulin providing that Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride for Injection. In September 2008, the FDA approved a revised package insert or label for Remodulin providing that Remodulin “must be diluted with either Sterile Water for Injection, or 0.9% Sodium Chloride Injection or Flolan⁷ Sterile Diluent for Injection” prior to intravenous administration.

A central venous catheter “is a catheter that’s tunneled under the skin, implanted into the vein.” The inserted tip of the catheter “is located near the heart and it comes out of [the patient’s]

⁷ Flolan® is a third party competitive product, containing epoprostenol, also approved for treating pulmonary hypertension. The “Sterile Diluent for Flolan,” (“SDF” or “Flolan diluent”) is a solution containing glycine and having a pH greater than 10 that physicians or patients may use to dilute Flolan prior to intravenous infusion.

chest wall.” Though it provides “direct access to [the] circulatory system” this method of administration causes “increased risk of bloodstream infection because of intrusion of bacteria.” (Tr. 479:24-480:9 (Zaccardelli), May 8, 2014; *see also* Tr. 1087:4-7 (Roberts), May 13, 2014; Tr. 1168:8-11 (McCoy), May 14, 2014.) Bloodstream infections are potentially fatal events for patients with PAH because these patients “have a very tenuous physiology and are prone to getting much worse very quickly, and having organ dysfunction like renal failure or death.” (Tr. 323:2-8 (White), May 7, 2014.) Additionally, there is “a large expenditure of healthcare resources” involved in treating a patient with a BSI. (Tr. 1670:14-1671:11 (White), May 16, 2014; *see also* Tr. 1061:22-1062:1 (Roberts), May 13, 2014.) Treatment for a BSI involves initial treatment in an emergency room with antibiotics, insertion of a temporary catheter followed by monitoring in a hospital’s intensive care unit, replacement of the permanent catheter, and finally several weeks of antibiotics following discharge from the hospital. (Tr. 323:2-324:5 (White), May 7, 2014; *see also* Tr. 1670:14-1671:11 (White), May 16, 2014.)

In April 2006, UTC’s Remodulin labeling committee noted “an increased rate of serious infection” in intravenous Remodulin users. (PTX-807 at UTC-Sand-Rem 00904244-45; *see also* Tr. 476:3-478:7 (Zaccardelli), May 8, 2014.) Around September 2006, Dr. Robyn Barst, MD, contacted UTC and the CDC to inform them that she was observing increased bloodstream infections in her intravenous Remodulin patients. (Tr. 478:8-21 (Zaccardelli), May 8, 2014; *see also* Tr. 324:9-325:2 (White), May 7, 2014; Tr. 1043:18-22 (Roberts), May 13, 2014; PTX-995 at UTC-Sand-Rem 01169629.) In late 2006 and early 2007, the “CDC conducted a retrospective investigation with the assistance of several state health departments and the cooperation of seven PAH treatment centers to determine the relative rates of BSI in a sample of patients treated with IV treprostinil and IV epoprostenol during 2003–2006.” (PTX-995 at UTC-Sand-Rem 01169629; *see also* Tr. 326:3-10 (White), May 7, 2014; Tr. 478:24-479:10 (Zaccardelli), May 8, 2014.) In March 2007, the CDC released a historical survey reporting “pooled mean rates of BSI (primarily gram-negative BSI) were significantly higher for patients on treprostinil [Remodulin] than for those on epoprostenol [Flolan].” (PTX-995 at UTC-Sand-Rem 01169629; *see also* Tr. 326:11-327:16 (White), May 7, 2014; Tr. 680:19-681:6 (Miller), May 9, 2014.) The CDC Survey offered

three “hypotheses ... that might explain the difference” in BSI rates: (1) “differences in practices involved in the preparation and storage of the two agents”; (2) “differences in infection-control practices involved in central venous catheter and infusion-set care”; and (3) “differences in the anti-inflammatory activity of the agents.” (PTX-995 at UTC-Sand-Rem 01169630.) The authors⁹ of the CDC Survey stated, “the cause of this difference [in BSI rates] is unclear.” The authors also stated, “[f]urther investigation is needed to identify the causes of the differences identified and to determine if these results are found at other PAH centers.” (PTX-995 at UTC- Sand-Rem 01169630.) The CDC Survey “didn’t identify any solution” for the bloodstream infection risks identified in the article. (Tr. 327:17-328:9 (White), May 7, 2014.) The CDC Survey doesn’t say anything about the different diluents used with Remodulin and Flolan. (Tr. 681:7-9 (Miller), May 9, 2014; Tr. 1040:6-1041:2 (Roberts), May 13, 2014; *see generally* PTX-995.) The CDC Survey concluded: “Until further information is available, clinicians who administer these drugs should be aware of the potential differences in BSI risk, particularly regarding infections caused by gram-negative organisms, which can be difficult to treat and can lead to substantial morbidity and mortality.” (PTX-995 at UTC-Sand-Rem 01169630; *see also* Tr. 327:17-328:9 (White), May 7, 2014.)

Following the CDC Survey, there was “general awareness and attention to the matter” of BSIs with Remodulin. It was also “brought up in front of the scientific leadership committee of the Pulmonary Hypertension Association.” (Tr. 486:2-13 (Zaccardelli), May 8, 2014; *see also* Tr. 328:10-14 (White), May 7, 2014.) Physicians in the field offered initial hypotheses for the difference in infection rates, including: that “catheter care guidelines at different sites were variable”; that Remodulin has a multi-use vial while Flolan has a single use vial; that Remodulin may be stored at room temperature; and “differences between treprostinil and epoprostenol, related to inflammatory impacts or immunosuppressive capabilities.” (Tr. 486:2-487:20 (Zaccardelli), May 8, 2014.) While “[t]here was a lot of intensive focus on catheter care guidelines,” the industry was not focused on the significant role that diluents would come to play

⁹ The CDC Survey lists multiple authors and was conducted with the assistance of experts in the care of pulmonary hypertension. (PTX-995 at UTC-Sand-Rem 01169629; Tr. 326:12-327:16 (White) May 7, 2014.)

in administering IV Remodulin and Flolan. .”

UTC began to investigate the BSI problem early in the fall of 2006, following the contact from Dr. Barst. As part of this investigation, Roger Jeffs and David Zaccardelli discussed differences between Flolan and Remodulin. (Tr. 482:12-482:24, 490:14-491:5 (Zaccardelli), May 8, 2014.) Among those differences, Drs. Jeffs and Zaccardelli noted “that Remodulin was at the time administered by being diluted with either saline or sterile water for injection, whereas Flolan was specifically diluted with Sterile Diluent for Flolan,” which they thought could possibly have an effect on BSIs. (Tr. 482:12-24 (Zaccardelli), May 8, 2014.)

In September of 2006, UTC “engaged an infectious disease expert,” Dr. Ralph Corey of Duke University. Dr. Corey did not “ha[ve] any experience with pulmonary hypertension with Remodulin, or with Flolan,” and United Therapeutics educated him about Flolan and Remodulin and its administration. Thereafter, Dr. Corey produced a report, in which he wrote: “Does the very high pH of epoprostenol inhibit bacterial growth even after dilution; unfortunately after dilution the pH of the infusate in the intravenous catheter is unknown; the pH of treprostinil is 7 throughout the infusion system.” (PTX-843 at UTC-Sand-Rem 01084360.) Dr. Corey included this paragraph in his report “as an outgrowth of conversations [Drs. Zaccardelli and Jeffs] had with him” in order to provide United Therapeutics with “a comprehensive review.” (Tr. 495:2-21 (Zaccardelli), May 8, 2014.)

In February and March of 2007, Dr. Zaccardelli hired a contractor to “test the effect of the diluent on the bacteria and on bloodstream infections” by “assessing the stability or compatibility and antimicrobial effectiveness of treprostinil or Remodulin with Flolan diluent.” (Tr. 500:10-21, 502:1-506:8 (Zaccardelli), May 8, 2014; PTX-491 at UTC-Sand-Rem 00000082-83; PTX-1076 at UTC-Sand-Rem 00000142.) On or about June 5, 2007, Dr. Zaccardelli received a formal report showing results of the antimicrobial effectiveness testing for Remodulin diluted with Sterile Diluent for Flolan. (Tr. 506:1-21 (Zaccardelli), May 8, 2014; PTX-500 at UTC-Sand-Rem 00000859, 868, and 871-72.) Reviewing these test results, Drs. Zaccardelli and Jeffs “noted that the reduction in gram negative bacteria seemed to be quicker, faster and more dramatic than the gram positive” and “were surprised a[t] how dramatic it was.” (Tr. 506:1-508:20 (Zaccardelli),

May 8, 2014; PTX-500 at UTC-Sand-Rem 00000859, 868, and 871-72.) Drs. Jeffs and Zaccardelli filed a patent application based on these research results, which issued as the '007 patent.

F. U.S. Patent No. 7,999,007

The '007 patent, entitled "Buffer solutions having selective bactericidal activity against gram negative bacteria and methods of using same," was issued by the PTO on August 16, 2011. The '007 patent expires on March 29, 2029. The named inventors on the '007 patent are Roger Jeffs and David Zaccardelli. The application that matured into the '007 patent was a continuation of application no. 12/205,200, filed on September 5, 2008, and claims priority to Provisional Application No. 60/970,716, filed on September 7, 2007. United Therapeutics is the owner of the '007 patent by assignment.

United Therapeutics is asserting claims 1-5, 7-17, 19-21, and 23 (the "asserted claims") against Sandoz. The asserted claims can be divided into three groups: two sets of method claims based on independent claims 1 and 11, respectively, and a composition claim, claim 23, which depends on independent claim 22. The first set of method claims, namely claims 1-5, 7-10 and 21, are generally directed to methods of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation. The second set of method claims, namely claims 11-17 and 19-20, are generally directed to methods of reducing the occurrence of blood stream infections by administering solutions that reduce gram negative bacteria and inhibit the growth of gram positive bacteria.

1. Asserted Claims

The asserted claims are reproduced in pertinent part below:

Claim 1

Independent claim 1 is representative of this group of claims, namely claims 1-5, 7-10 and 21. Claim 1 recites:

A method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium, the method comprising supplying the active agent with a buffer comprising glycine and having a pH of greater than 10 with low buffer capacity.

(Final Pretrial Order, Ex. 1 (Stipulated Facts) [ECF No. 179-1].)

As previously noted, the Court held a *Markman* hearing on May 20, 2013 (the “2013 *Markman* Hearing”) and on June 25, 2013, issued an Order construing the disputed terms. *See* ECF No. 95. Therein, the Court determined that no construction was required for the disputed term “A method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation” as used in Claim 1 and the term should be accorded its plain and ordinary meaning. *Id.* at 15-16, 25. The Court further determined that no construction was required for the disputed term “the method comprising supplying the active agent with a buffer comprising glycine and having a pH of greater than 10 with low buffer capacity” as used in Claim 1 and the term should be accorded its plain and ordinary meaning. *Id.* at 17, 25.

Claim 11

Independent claim 11 is representative of the second group of claims, namely claims 11-17 and 19-20. Claim 11 recites:

A method of reducing the occurrence of blood stream infections in a mammal being treated with an active agent comprising administering to the mammal the active agent with a buffer comprising glycine and having a pH of greater than 10, wherein the active agent is selected from the group consisting of treprostinil and treprostinil sodium, and wherein the administration reduces the gram negative bacteria and inhibits the growth of gram positive bacteria.

(Agreed Fact No. 58, [Proposed] Final Pretrial Order, Ex. 1 (Stipulated Facts) [ECF No. 179-1].)

Following the 2013 *Markman* Hearing, the Court determined that no construction was required for the disputed term “wherein the administration reduces the gram negative bacteria and inhibits the growth of gram positive bacteria” as used in claim 11 and the term should be accorded its plain and ordinary meaning. (ECF No. 95 at 21, 25.)

Claim 16

Claim 16 recites “[t]he method of claim 11, wherein the buffer has a pH between about 10 to about 12 with low buffer capacity.”

Claim 23

Claim 23 is a composition claim that depends on independent claim 22. Claim 22 recites:

A pharmaceutical composition comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium in a solution comprising glycine and having a pH greater than 10.

(Agreed Fact Nos. 60, 61, Final Pretrial Order, Ex. 1 (Stipulated Facts) [ECF No. 179-1].)

Following the 2013 *Markman* Hearing, the Court construed disputed term “a pH between about 10 to about 12” as used in claims 4 and 16 to mean “a pH between 10 and 12 with nominal and accepted variations recognizing the inherent inaccuracies in calculations and measurements.” ECF No. 95 at 24, 25.

G. Sandoz’s Generic ANDA Product

United Therapeutics holds an approved NDA (No. 21-272) for Treprostinil Sodium Injection, which United Therapeutics markets and sells under the federally registered trademark Remodulin. On December 2, 2011, Sandoz filed Abbreviated New Drug Application No. 203649 with the FDA seeking approval to commercially manufacture, use and sell its Treprostinil Injection product in 10 mg/ml concentration for the treatment of pulmonary arterial hypertension. (PTX 250 at Sandoz-Trep0000010).

Sandoz sent Plaintiff a letter dated February 3, 2012 stating that it had submitted ANDA No. 203649 to the FDA under β 505(j) of the Act seeking approval to engage in the commercial manufacture, use, or sale of the product described in ANDA No. 203649. Sandoz's notice letter stated that Sandoz's ANDA contained a certification that, *inter alia*, the patents-in-suit were invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, or sale of the drug product described in ANDA 203649. UTC brought suit against Sandoz on March 14, 2012, within forty-five days of receiving Sandoz's notice letter, alleging infringement of the patents-in-suit.

On December 7, 2012, Sandoz filed an amendment to ANDA No. 203649 with the FDA seeking additional approval to commercially manufacture, use, and sell generic Remodulin at

strengths of 1 mg/mL, 2.5 mg/mL, and 5 mg/mL before the expiration of UTC's Remodulin patents. On January 16, 2013, UTC filed a second suit against Sandoz for patent infringement, based upon Sandoz's amended ANDA filing.¹⁰

Sandoz's ANDA represents to the FDA that the identical formulations between its ANDA Product and Remodulin result in "therapeutic equivalence." (PTX-334 at Sandoz-Trep 0010814; Tr. 845:22-25 (Skoumbourdis), May 12, 2014.) Sandoz's ANDA specifies that the 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL formulations of its ANDA Product contain identical quantities of active and inactive ingredients as the 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL formulations of Remodulin, respectively. (PTX-334 at Sandoz-Trep 0010814-815; Tr. 578:4-580:1 (Miller), May 8, 2014.)

In an April 25, 2013 ANDA Amendment, Sandoz submitted a statement pursuant to 21 U.S.C. § 355(j)(2)(A)(viii), stating that the '007 patent does not claim uses for the treprostinil sodium ANDA products for which Sandoz is seeking FDA approval, namely use of treprostinil sodium diluted with sterile water or 0.9% sodium chloride for intravenous administration for the treatment of pulmonary hypertension. (ECF No. 218, Exhibit 1 to Pretrial Order, Stipulated Fact No. 72). In this April 25, 2013 ANDA Amendment, Sandoz carved out of its proposed label all references and any instruction to use Sterile Diluent for Flolan as a diluent for intravenous administration of treprostinil. (PTX 402 at Sandoz-Trep0048791, 48806-7; Skoumbourdis, Trial Tr. at 847:9-12). Following this carve out, Sandoz's proposed label now instructs that Sandoz's treprostinil product must be diluted with sterile water or 0.9% sodium chloride for intravenous administration. (PTX 167 at Sandoz-Trep0083447; Roberts, Trial Tr. 1035:16-21; McCoy, Trial Tr. 1150:9-12).

D. Witnesses at Trial

Credibility Determinations

With respect to the witnesses appearing at trial, the Court has had the opportunity to hear

¹⁰ The 30-month stay imposed by 21 U.S.C. § 355(j)(5)(B)(iii) on the FDA with respect to granting final approval of ANDA No. 203649 expires on or around August 3, 2014. However, Sandoz has since certified to the FDA that they will not launch before the date of expiration of the '222 patent in October 2014. *See supra* FN 1.

all their testimony and observe their demeanor. Having done so, the Court has made certain credibility determinations as well as determinations relating to the appropriate weight to accord various testimony. Such determinations are reflected in the factual findings set forth below.

Expert Witnesses

R. James White, M.D.

R. James White, M.D. was offered by UTC and accepted as an “expert in ...pulmonary arterial hypertension.” (Tr. 308:10-14 (White), May 7, 2014.) Dr. White is an associate professor at the University of Rochester. (Tr. 303:21-23 (White), May 7, 2014.) Dr. White focuses almost all of his professional efforts on the care of patients with PAH, and currently oversees the care of about 250 patients with PAH. (Tr. 304:24-305:1 (White), May 7, 2014.) In addition to his clinical work, Dr. White maintains a small laboratory where he works to understand the mechanisms of PAH and studies new ways to treat the disease. (Tr. 307:7-12 (White), May 7, 2014.) Dr. White is a member of the American Thoracic Society and the Pulmonary Hypertension Association, and has authored at least a dozen papers on the subject of PAH. (Tr. 307:13-20 (White), May 7, 2014; *see generally* PTX-129.)

Michael J. Miller, Ph.D.

Michael J. Miller, Ph.D. was offered by UTC and accepted as an expert for the '007 patent in the field of microbiology and parenteral pharmaceuticals, including sterility issues and antimicrobial effectiveness testing. (Tr. 569:10-17 (Miller), May 8, 2014.) Dr. Miller obtained a Ph.D. in microbiology and biochemistry from Georgia State University in Atlanta in 1988. (Tr. 563:17-21 (Miller), May 8, 2014; PTX-118.) Dr. Miller has nearly twenty years' industry experience in microbiology and the sterility of parenteral drug products. (Tr. 563:17-564:15 (Miller), May 8, 2014; *see generally* PTX-118.) Dr. Miller's area of expertise “is in pharmaceutical microbiology, specifically sterility assurance, contamination control, antimicrobial effectiveness, and the microbiological strategies associated with pharmaceutical manufacturing and drug development.” (Tr. 562:6-10 (Miller), May 8, 2014.)

Robert M. Williams, Ph.D.

Dr. Robert Williams was offered by UTC and accepted as an expert in “organic chemistry, synthesis of complex organic molecules, including Pauson-Khand reactions and protecting groups.” (Tr. 870:23-871:4 (Williams), May 12, 2014.) Dr. Robert Williams has a Ph.D. in chemistry from the Massachusetts Institute of Technology, worked with Nobel Laureate R.B. Woodward at Harvard for his post-doctorate fellowship, and has over 30 years of experience in organic chemistry and development of synthetic routes for active pharmaceutical ingredients. (Tr. 863:16-870:14 (Williams), May 12, 2014; PTX-139.)

Paul Aristoff, Ph.D.

Dr. Paul A. Aristoff was offered by UTC and accepted as an expert “in the field of organic and medicinal chemistry, synthesis of prostacyclin analogs, and the subject matter of the ’117 patent.” (Tr. 1715:18-1716:7 (Aristoff), May 16, 2014.) Dr. Paul A. Aristoff has a B.S. and M.S. in chemistry from Northwestern University, received a National Science Foundation (“NSF”) fellowship for his Ph.D. in chemistry at the California Institute of Technology, and worked at the Swiss Federal Institute of Technology in Zurich, Switzerland on an NSF post-doctoral fellowship. (Tr. 1711:11-20 (Aristoff), May 16, 2014; PTX-102.) Dr. Aristoff has over 35 years of experience in organic chemistry and development of synthetic routes for active pharmaceutical ingredients, with extensive experience in the organic synthesis of prostacyclin analogs. (Tr. 1710:17-1711:01; 1711:11-1713:17 (Aristoff), May 16, 2014; PTX-102.) Dr. Aristoff is the inventor of treprostinil, and spent about thirty years at the Upjohn Company (“Upjohn”) and its related companies designing and synthesizing stable prostacyclin analogs. (Tr. 1713:15-17, 1714:9-21 (Aristoff), May 16, 2014; PTX-102.) Dr. Aristoff is the inventor or co-inventor of about 30 U.S. patents, including patents for three pharmaceutical compounds that were approved by the FDA, which he developed during his 30 years at Upjohn. (Tr. 1714:9-17 (Aristoff), May 16, 2014; PTX-102.)

Richard Gering, Ph.D.

Dr. Richard Gering was offered by UTC and admitted by the Court as an expert in the field

of economics and economic analysis for purposes of assessing commercial success in this case. (Tr. 1915:1-9 (Gering), May 19, 2014; PTX-109.) Dr. Richard Gering is a partner at Eisner Amper, an accounting and consulting firm primarily based in New Jersey, New York and Pennsylvania. (Tr. 1912:7-10 (Gering), May 19, 2014; PTX-109.) Dr. Gering has a Bachelor's of Commerce from University of Natal in economics and business administration with an honors in economics and a Master's in Ph.D. in economics from the University of Maryland. Dr. Gering has a C.L.P., which is a Certified Licensing Professional, a certification granted by the licensing executive society. (Tr. 1913:12-19 (Gering), May 19, 2014; PTX-109.) Dr. Gering has been qualified as an expert witness in more than 25 trials. (Tr. 1914:18-19 (Gering), May 19, 2014; PTX-109.)

Stephen Buchwald, Ph.D.

Dr. Buchwald is a professor of chemistry who addressed (1) UTC's allegations of infringement of the '117 patent under the doctrine of equivalents and (2) the invalidity of the '117 patent. Testifying on behalf of Sandoz, Dr. Buchwald was qualified as an expert in the field of synthetic organic chemistry. (Buchwald, Trial Tr. 1202:25-1203:6). Dr. Buchwald is the Camille Dreyfuss Professor of Chemistry at the Massachusetts Institute of Technology, where he has taught since 1984. (Buchwald, Trial Tr. 1200:17-20). Dr. Buchwald received a PhD from Harvard and later completed a post-doctoral fellowship at the California Institute of Technology. (Buchwald, Trial Tr. 1200:19-23).

Christopher McCoy, Pharm.D.

Dr. McCoy is a pharmacist who addressed UTC's allegations of induced infringement of the '007 patent. Testifying on behalf of Sandoz, Dr. McCoy was qualified as an expert in the field of pharmaceuticals, developing and formulating pharmaceutical products and assisting in the treatment of patients with pulmonary arterial hypertension. (McCoy, Trial Tr. 1146:5-13). Dr. McCoy is the Clinical Pharmacy Director for Antimicrobial Stewardship at Beth Israel Deaconess Medical Center in Boston. (McCoy, Trial Tr. 1143:1-5). Dr. McCoy received a doctorate in

pharmacy from the Massachusetts College of Pharmacy. (McCoy, Trial Tr. 1142:19-25). He is also an assistant professor at Northeastern University. (McCoy, Trial Tr. 1144:5-7).

David Roberts, M.D.

David Roberts is a physician who addressed UTC's allegations of induced infringement of the '007 patent, as well as secondary considerations of non-obviousness with respect to the '007 patent. Testifying on behalf of Sandoz, Dr. Roberts was qualified as an expert in the field of pulmonary hypertension. (Roberts, Trial Tr. 1028:16-22). Dr. Roberts is a Director of Faculty Development at the Beth Israel Deaconess Medical Center's Pulmonary and Critical Care Division. (Roberts, Trial Tr. 1025:14-17). He is also an Associate Professor of Medicine at Harvard Medical School. (Roberts, Trial Tr. 1026:2-4). Dr. Roberts's work at Beth Israel includes treating patients with pulmonary arterial hypertension and teaching trainees how to interpret clinical trials concerning PAH. (Roberts, Trial Tr. 1026:19-1027:24). Dr. Roberts received his medical degree from Harvard Medical School and he went on to obtain additional training in pulmonary medicine. (Roberts, Trial Tr. 1025:11-22).

James Thomson, Ph.D.

Dr. Thomson is a pharmaceutical formulation scientist who addressed the invalidity of the '007 patent. Testifying on behalf of Sandoz, Dr. Thomson was qualified as an expert in the field of pharmaceutical formulations. (Thomson, Trial Tr. 1483:13-19). Dr. Thomson is currently a self-employed consultant in the pharmaceutical industry. (Thomson, Trial Tr. 1481:16-17). Prior to consulting, Dr. Thomson worked at four major pharmaceutical companies: Cetus Corporation, Synergen, Inc., North American Biologicals Inc., and Chiron Corporation. At each of these companies, Dr. Thomson worked in process and product development, developing pharmaceutical preparations, including testing formulations in animal models and conducting clinical trials to support the commercialization of pharmaceutical products. (Thomson, Trial Tr. 1481:22-1482:21). Dr. Thomson holds a PhD in biochemistry from the University of Washington and completed a post-doctoral fellowship at the University of Wisconsin. (Thomson, Trial Tr.

1481:18-21; DTX-104).

Thomas Vander Veen, Ph.D.

Dr. Vander Veen is an economist who addressed UTC's allegations regarding secondary consideration of non-obviousness of commercial success for both the '117 patent and the '007 patent. Testifying on behalf of Sandoz, Dr. Vander Veen was qualified as an expert in the field of economics to testify as to his assessment of commercial success in this case. (Vander Veen, Trial Tr. 1299:11-17). Dr. Vander Veen is a Managing Director at Navigant Economics, a global economic consulting firm. Dr. Vander Veen holds a PhD from in economics from Brown University. (Vander Veen, Trial Tr. 1297:11).

II. Discussion and Conclusions of Law

The Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions and the applicable law, the Court concludes that: (1) UTC has failed to prove by a preponderance of the evidence that Sandoz's proposed ANDA product will induce infringement of the asserted claims of the '007 patent; (2) Sandoz has failed to prove by clear and convincing evidence that the asserted claims of the '007 are invalid; (3) UTC has proved by a preponderance of the evidence that Sandoz's ANDA product will infringe and induce infringement of the asserted claims of the '117 patent; and (4) Sandoz has failed to prove by clear and convincing evidence that the asserted claims of the '117 patent are invalid.

The Court's reasoning follows.

A. Person of Ordinary Skill in the Art

The scope and analysis of the patents-in-suit is to be undertaken by the hypothetical "person of ordinary skill in the art" or "skilled artisan."

1. The '007 Patent

Plaintiff's expert, Dr. Miller proposed that, "at the time of the '007 invention, a person of ordinary skill in the art would have had at least a Bachelor's Degree in microbiology, chemistry or

a related field, with at least two years of postgraduate experience in contamination control, or sterility assurance for pharmaceuticals and/or medical devices.” (Tr. 571:7-19 (Miller), May 8, 2014.)

Sandoz’s expert, Dr. Thomson, defined a person of ordinary skill in the art as someone “hav[ing] a fairly high level of education, a Ph.D. or possibly an M.D., and additional work experience in the appropriate fields of either drug development, pharmaceutical formulation, possibly microbiology, biochemistry and medicine, or alternatively a Bachelor’s, Master’s degree and additional years of work experience.” (Tr. 1484:14-23 (Thomson), May 15, 2014.)

Whereas Plaintiff’s expert, Dr. Miller, “generally agree[d] with Dr. Thomson’s opinion”, and testified that his “standard is consistent with [Dr. Thomson’s],” the Court has determined that a person having ordinary skill in the art relating to the inventions claimed by the ‘007 patent, at the time that the claimed inventions were made, would “have a fairly high level of education, a Ph.D. or possibly an M.D., and additional work experience in the appropriate fields of either drug development, pharmaceutical formulation, possibly microbiology, biochemistry and medicine, or alternatively a Bachelor’s, Master’s degree and additional years of work experience.” (Tr. 1484:14-23 (Thomson), May 15, 2014.)¹¹

2. The ‘117 Patent

Based on the agreement of experts for both parties, the Court finds that at the time of the ‘117 invention, a person of ordinary skill in the art in the field of the invention would have held a Ph.D. in chemistry (or a related field) or a bachelor’s or master’s degree in chemistry (or a related field) with at least three years of post-graduate experience in organic synthesis. (Tr. 872:4-11 (Williams), May 12, 2014; Tr. 1717:7-15 (Aristoff), May 16, 2014.)

B. Infringement of the ‘007 Patent

As previously noted, UTC contends that Sandoz’s proposed ANDA product will induce infringement of the asserted claims of the ‘007 patent. Specifically, UTC contends that Sandoz’s

¹¹ Dr. Miller further testified that “even if [he] applied Dr. Thomson’s standard [his] opinions would not have changed.” (Tr. 572:12-20 (Miller), May 8, 2014.)

proposed label “actively induces” physicians to prescribe the Sterile Diluent for Flolan for use in conjunction with Sandoz’s ANDA product for intravenous administration. Such use, the parties agree, would directly infringe each of the asserted claims of the ‘007 patent. In spite of a relevant carve out by Sandoz, which eliminated any mention of the Sterile Diluent for Flolan, UTC argues that the Warnings and Precautions in Sandoz’s generic product label are “so unusual” and “so severe” that they amount to an implicit instruction to physicians to dilute Sandoz’s generic product with Sterile Diluent for Flolan. *See* Pls. Post-Trial Br. at 7-12. UTC argues that even with Sandoz’s current carved-out label, “some nurses, doctors and other healthcare providers or patients may nevertheless elect to prescribe or use the Flolan Sterile Diluent to dilute Sandoz’s ANDA product for intravenous administration,” as a preventative measure against BSIs, after undertaking research “encouraged” by scientific references present in the Warnings and Precautions section of Sandoz’s generic label. (Tr. 1064:5-18 (Roberts), May 13, 2014.)

Sandoz maintains that it has carved out of its proposed label any instruction to use Sterile Diluent for Flolan as a diluent for intravenous administration of treprostinil, and further contends that the remaining statements in its proposed generic label, along with the other evidence presented in this case, are insufficient to show that Sandoz has a specific intent to encourage physicians to dilute Sandoz’s ANDA products with Sterile Diluent for Flolan. Sandoz further asserts that its proposed label is directed entirely to non-infringing uses, namely subcutaneous use and dilution with either water or saline for intravenous administration. Sandoz provides that its own proposed label provides the following “explicit, non-infringing instructions on how to reduce the risk of blood stream infections: (1) to administer treprostinil subcutaneously as the preferred mode of administration, and (2) to instruct patients that aseptic technique must be used in the preparation and administration of treprostinil injection.” In light of such substantial non-infringing uses, Sandoz argues that the Court cannot infer an intent to induce infringement of the ‘007 patent.

For the reasons that follow, the Court concludes that UTC has failed to establish that Sandoz’s proposed generic label would induce infringement of the asserted claims of the ‘007 patent.

1. Legal Standard

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Courts employ a two-step analysis in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly construed claims with the accused infringing product. *See Tanabe Seiyaku Co. v. United States Int'l Trade Comm'n*, 109 F.3d 726, 731 (Fed. Cir. 1997) (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370, 116 S. Ct. 1384, 134 L. Ed. 2d 577 (1996)). If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Id.* at 1552 n.9.

The patent owner has the burden of proving by a preponderance of the evidence that "every limitation of the patent claim asserted to be infringed is found in the accused [method], either literally or by equivalent." *SmithKline Diag., Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). Per this standard, a patent owner does not have to produce "definite" proof of infringement, but must instead demonstrate that "infringement was more likely than not to have occurred." *See Warner-Lambert Co. v. Teva Pharms., USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005) (citing *Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001)).

In the ANDA context, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2)(A). Here, courts are tasked with assessing what the ANDA will likely market if its application is approved--

recognizing that this has not yet occurred--and, in so doing, requires examining the ANDA application and the extensive materials submitted in its support. To this end, the infringement analysis is hypothetical and requires comparing the asserted claims against the product that is likely to be sold should the FDA approve the application.

More specifically, as it relates to the instant matter, 35 U.S.C. β 271(b) states that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. β 271(b). Inducement requires "actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 675 (Fed. Cir. 1990). In the Hatch-Waxman context, "[s]tatements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement" for purposes of inducement to infringe under 35 U.S.C. β 271(b). "A defendant who is aware of a patent and supplies a product to a customer with instructions for use, which when followed lead to infringement, has encouraged acts constituting direct infringement." *3M Co. v. Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002).

Importantly, however, mere knowledge of possible infringement does not constitute inducement. Rather, the patentee must prove that the defendant's actions "induced infringing acts and that [the defendant] knew or should have known that [its] actions would induce actual infringement." *See Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990). In ANDA cases, the "pertinent question is whether the proposed label instructs users to perform the patented method," as well as "promote[s] or "encourage[s]" others to practice the patented method. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (citing *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)); *see also Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003).

Where there is no literal infringement, there may still be infringement under the doctrine of equivalents. "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733, 122 S. Ct. 1831, 152 L. Ed. 2d 944 (2002). A patentee may prove infringement under the

doctrine of equivalents "by showing on a limitation by limitation basis that the accused product performs substantially the same function in substantially the same way with substantially the same result as each claim limitation of the patented product." *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009).

As previously noted, United Therapeutics contends that Sandoz's ANDA product will induce infringement of the asserted claims of the '007 patent. To prove indirect infringement, UTC must prove by a preponderance of the evidence that: (1) administering Sandoz's ANDA product in SDF for intravenous administration would directly infringe each of the asserted claims of the '007 patent and (2) that Sandoz's proposed label "actively induces" physicians to prescribe use of the Sterile Diluent for Flolan to dilute Sandoz's ANDA product for intravenous administration.

Sandoz concedes that administering generic Remodulin in SDF would directly infringe the '007 asserted claims.¹²

2. Sandoz's ANDA label does not induce physicians to directly infringe the asserted claims of the '007 patent

UTC contends that Sandoz's proposed ANDA label will "actively induce" physicians to prescribe the Sterile Diluent for Flolan to dilute Sandoz's ANDA product for intravenous administration. The pertinent parts of Sandoz's proposed label are reproduced below.

The first page of the proposed label, entitled "Highlights of Prescribing Information," states as follows:

¹² The Court notes the following facts for the record: (1) In both its pre-trial brief and opening argument, Sandoz asserted that the only issue regarding infringement of the '007 patent is whether Sandoz *would induce* infringement. (Tr. 280:23–25 (Sandoz Opening Argument), May 7, 2014 ("This case is only about the first prong of the inducement analysis, whether Sandoz will actively induce infringing conduct."); Sandoz Pretrial Br. at 2; see also Tr. 489:13–14 (Objection by Sandoz's Counsel) ("The only question is are we [*i.e.*, Sandoz] inducing infringe[ment].") (2) Sandoz presented no testimony that the administration of Sandoz's ANDA Product in SDF would not directly infringe the '007 patent. (3) Sandoz did not attempt to refute Plaintiff's expert's analysis showing how administering Sandoz's ANDA product with SDF meets all the limitations of the '007 Asserted Claims. (Tr. 575:19–576:19; 577:22–580:1; 580:22–591:25; 601:9–606:24 (Miller), May 8, 2014.) (4) Finally, Defendant's own expert, Dr. Roberts, testified that some physicians may dilute Sandoz's ANDA product in SDF, which would directly infringe the '007 patent. (Tr. 1064:5–18 (Roberts), May 13, 2014.)

Administration

Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if subcutaneous infusion is not tolerated.

(PTX 167 at Sandoz-Trep0083444). For intravenous administration, the current version of Sandoz's proposed label states:

Intravenous Infusion

Treprostinil Injection must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection and is administered intravenously by continuous infusion via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery.

(PTX 167 at Sandoz-Trep0083447 (original emphasis); Roberts, Trial Tr. 1036:16-21).

Sandoz's proposed label also contains warnings in several places regarding the risk of blood stream infections associated with the intravenous administration of treprostinil. With respect to this risk, Sandoz's proposed label further provides explicit, non-infringing instructions on how to reduce the risk of blood stream infections: (1) to administer treprostinil subcutaneously as the preferred mode of administration, and (2) to instruct patients that aseptic technique must be used in the preparation and administration of treprostinil injection. Again, the pertinent provisions are set out below. The first page of the label, which sets out "Highlights of Prescribing Information," contains the following warning:

WARNINGS AND PRECAUTIONS

Chronic intravenous infusions of treprostinil injection are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. (5.1)

(PTX 167 at Sandoz-Trep0083444). Section 5 ("Warnings and Precautions") further warns of:

5.1 Risks Attributable to the Drug Delivery System

Chronic intravenous infusions of treprostinil injection are delivered using an

indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use.

(PTX 167 at Sandoz-Trep0083450 (Section 5.1)). Similarly, Section 1.1 states:

[Treprostinil injection] may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted [see Warnings and Precautions (5.1)].

(PTX 167 at Sandoz-Trep0083445). Sandoz's proposed label further instructs, as follow:

17 PATIENT COUNSELING INFORMATION

Patients receiving treprostinil injection should be given the following information:

* * *

In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of treprostinil injection.

(PTX 167 at Sandoz-Trep0083459).

UTC contends that the warning in Sandoz's proposed label regarding the risk of blood stream infections and the information about blood stream infections identified in a CDC survey is an "implicit" instruction to physicians to prescribe Sterile Diluent for Flolan. UTC's expert, Dr. White, testified that the warning found in Sandoz's proposed label about blood stream infections "is so unusual and so severe, that it is going to instruct physicians as big as a neon sign that they need to learn more about how to reduce the incidence of bloodstream infections to protect their patients from a potentially fatal outcome of their prescription." (White, Trial Tr. 359:15-20).

UTC asserts the label's warnings and references, taken together, could set in motion a chain of events that might lead some physicians to prescribe the Sterile Diluent for Flolan with Sandoz's generic treprostinil product, based on recommendations made in the scholarly literature that, UTC argues, is likely to turn up in a provider's subsequent research. Specifically, UTC argues that some physicians may decide, based on the warnings in Sandoz's label, to (1) search for and review the CDC publication referenced, then, (2) search for and review the Rich, Zaccardelli and/or Kitterman articles recommending use of Sterile Diluent for Flolan and ultimately, as a result of this quest, (3) elect to prescribe Sterile Diluent for Flolan with Sandoz's generic treprostinil products.

Sandoz argues that that it cannot be liable for induced infringement because it has carved out any alleged instruction to infringing use, namely references to the use of Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium from its proposed label. (FF 82-83, 113, 116, 127). Specifically, Sandoz argues that Sandoz's label does not provide any instruction to use the Flolan diluent, the epoprostenol sodium diluent, or any other diluent or buffer containing glycine and having a pH greater than 10, with Sandoz's treprostinil sodium ANDA products. (FF 82-84, 113, 116-117, 127-128). Rather, Sandoz contends that the instructions in Sandoz's proposed ANDA label teach undisputedly non-infringing uses. Accordingly, Sandoz concludes that Sandoz cannot infringe by inducement under Section 271(b) as a matter of law because its amended label does not instruct others, such as physicians or end-users, to use a glycine buffer having a pH greater than 10 with treprostinil sodium. *DSU Med. Corp.*, 471 F.3d at 1305-06; *Warner-Lambert*, 316 F.3d at 1364; *AstraZeneca Pharmaceuticals LP v. Apotex Corp.*, 669 F.3d 1370, 1379-80 (Fed. Cir. 2012).

The Court agrees with Sandoz. The law of inducement requires a showing by UTC that Sandoz's ANDA label actually *instructs* physicians to dilute its product with Sterile Diluent for Flolan or some other high pH glycine buffer. At the outset, the Court acknowledges that Sandoz's label does not contain any explicit instruction to use the Flolan diluent, the epoprostenol sodium diluent, or any other diluent or buffer containing glycine and having a pH greater than 10, with Sandoz's treprostinil sodium ANDA products. Sandoz's label instructs physicians that

“continuous subcutaneous infusion is the preferred mode of administration, and further provides that, where intravenous use is necessary, its treprostinil injection product “must” be diluted with water or saline for intravenous administration. Each of these instructions is an undisputedly a non-infringing use. (Roberts, Trial Tr. 1035:9-1037:7; McCoy, Trial Tr. 1148:18-1149:16, 1149:23-1150:12; 1195:19-1196:11). Next, the Court finds that the warnings in Sandoz’s label do not amount to an implicit instruction. The Court notes that there is a rather significant difference between a warning and an instruction. A warning provides information regarding a potential risk. It does not prescribe a course of action. An instruction, on the other hand, is a statement directing one to take some action, such as how to avoid a potential adverse event. (McCoy, Trial Tr. 1149:2-22). Sandoz’s proposed label provides two explicit instructions on avoiding the risk of blood stream infections identified in the Warnings and Precautions sections of the label: Sandoz’s proposed label (1) directs physicians to use subcutaneous infusion as the preferred mode of administration and means to address the identified risk of blood stream infections associated with intravenous infusion and (2) further directs physicians to counsel patients on the use aseptic technique, in the preparation and administration of treprostinil injection, “in order to reduce the risk of infection”.

UTC’s theory would suggest that the absence of an instruction should be discounted in this instance, on the theory that a scholarly scavenger hunt—which *may* be incited by a reference in Sandoz’s proposed label, which *may* be undertaken by some physicians, and *may* ultimately result in a discovery which leads some physicians to prescribe SDF as a diluent for Defendant’s generic product, despite Defendant’s carve out—may constitute evidence of Sandoz’s intent to induce physicians to engage in infringing conduct.

In light of the bulk of the evidence admitted at trial suggesting that pulmonary hypertension drugs are prescribed by pulmonary hypertension specialists, the Court finds UTC’s scavenger hunt theory tenuous at best. UTCs expert, Dr. White gave significant testimony suggesting that inexperienced “practitioners” would be likely to conduct the scholarly scavenger hunt:

Q. So I think the pending question was what types of practitioners would read

this section [5.1] of the package insert?

A. Yes, Counselor. I think all practitioners would read this. If you were thinking about prescribing it, **if you were a nurse that was receiving an order in a hospital for the first time, if you were [a] pharmacist who was filling an order for the first time, any healthcare provider is going to read the very first paragraph of warnings and precautions.**

* * *

Q. Now, what would a – in your view, what would a less experienced practitioner do when reading this?

A. * * * **I think that a less experienced practitioner is going to feel even a greater onus to learn more about the risk for bloodstream infection,** potentially fatal bloodstream infection; and to then avail themselves of every technique, including closed-hub catheter system, waterproofing connection and SDF, in order to reduce the incidence of bloodstream infections, which might be fatal.

* * *

Q. Now, on cross-examination you also testified about a significant minority of doctors treating pulmonary hypertension; do you recall that?

A. I do.

Q. How often in your knowledge do inexperienced clinicians prescribe Remodulin?

A. Too frequently.

Q. And what would these – what would those inexperienced practitioners know about the BSI problems that we've been discussing today?

A. They would certainly not have firsthand knowledge of the events of 2006. Without the instruction of the label I think many of them would be unaware of a detailed study like the CDC survey. I can be sure that they would not have knowledge of the really nice contribution of Dunbar/Ivy, and they wouldn't know about the primary data from the Zaccardelli study, nor would they know about the Rich study. These – these would not be firsthand knowledge for them.

And so, for them to read the label and see this, and start using a search engine to learn more about it, would be in my mind a direct consequence of the severity of the warning on Sandoz's current package insert.

(White, Trial Tr. 363:14-21; 370:19-371:3; 408:7-409:3) (emphasis added). However, the Court finds Dr. White's testimony, and indeed UTC's stance, unpersuasive in light of contrary testimony given by Dr. Roberts who testified that he believed that it was "extraordinarily unlikely", indeed that "he had never heard of," "someone who doesn't have experience" inserting a central catheter in a patient and prescribing IV Remodulin, as well as the following testimony given by Dr. McCoy that prescription forms for Remodulin also require that certain specialized diagnostic criteria be filled in, which would need to be done by a pulmonary hypertension specialist:

THE COURT: Doctor, before you step down, at one point in time we were talking about the specialty pharmacies.

THE WITNESS: Yes.

THE COURT: And I thought you said that the only one that could submit a prescription to those pharmacies were PAH specialists.

THE WITNESS: Yes.

THE COURT: I haven't heard any testimony on PAH specialists; is that a Board-Certified group?

THE WITNESS: So that would be someone like Dr. Roberts who has additional training in pulmonary arterial hypertension. Even the UTC referral form and even within the Sandoz label, they recommend that these patients – that treprostinil only be prescribed by specialists in pulmonary hypertension.

THE COURT: How would the pharmacy know that?

THE WITNESS: So, Accredo would not have necessarily direct knowledge of their level of expertise, but I will say that within the referral form they require that certain diagnostic criteria be filled out, including the results of a – central catheter pressures, essentially to – and also diagnostic in terms of imaging. So I suppose someone could kind of just check boxes, but you'd still be required to kind of fill out the details of the diagnosis within the form.

(Roberts, Trial Tr. 1031:10-132:10; (McCoy, Trial Tr. 1197:8-1198:6). Even Dr. White himself admitted at trial that he is not going to prescribe Sterile Diluent for Flolan with Sandoz's generic

treprostinil product because of what Sandoz says in its label. (White, Trial Tr. 404:24-405:4 (Q. Now, you're not going to prescribe sterile diluent for Flolan with Sandoz's generic treprostinil product because of what Sandoz says in its label; correct? A. Me personally? Q. Yes. A. That's correct.")). Noting that Sandoz's proposed label specifically provides that its product should only be used by experienced pulmonary hypertension physicians, the Court finds that is likely to be true of other experienced pulmonary hypertension physicians who have formed their own independent medical judgment as to whether to prescribe Sterile Diluent for Flolan with their IV treprostinil patients. Given the attention that has been paid to the blood stream infection issue with IV treprostinil since 2006, the Court finds that physicians who are experienced in the diagnosis and treatment of pulmonary hypertension are unlikely to make a decision to prescribe Sterile Diluent for Flolan based on what Sandoz says, or in this case, allegedly alludes, in its label. *See* DTX-472 (September 25, 2006 "Dear Healthcare Provider" letter regarding the risk of blood stream infection issue associated with IV Remodulin.); DTX-456 (November 29, 2006 "Dear Healthcare Provider" letter); DTX-482 (March 6, 2007 "Dear Healthcare Provider" letter)).

This Court concludes that the warnings in Sandoz's proposed label are not instructions encouraging physicians to dilute Sandoz's ANDA product in Sterile Diluent for Flolan. The Court further concludes therefore, that there is no implicit or explicit instruction to infringe contained in Sandoz's proposed ANDA label. Sandoz's label provides explicit, non-infringing instructions on how to address the risk of blood stream infections. If some physicians nonetheless choose to prescribe Sterile Diluent for Flolan with Sandoz's ANDA product, the Court finds that they will do so based on their own independent belief that Sterile Diluent for Flolan provides a benefit for their patients. Sandoz's label does not instruct them to do so. It is not enough that "a user following the instructions may end up" practicing the patented method. *AstraZeneca L.P. v. Apotex, Inc.*, 633 F.3d 1043,1060 (Fed. Cir. 2010) (quoting *Vita-Mix Corp. v. Basic Holding Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)). Rather, the instructions must be such that a court can "infer from those instructions an affirmative intent to infringe the patent." *Id.*; *see also Novartis Pharma. Corp. v. Wockhardt*, Case No. 12-3967, 2013 U.S. Dist. LEXIS 152141, at 27-31 (D.N.J. Oct. 23, 2013) (Wigenton, D.J.) (dismissing inducement claims in the absence of a direction or

instruction to actively infringe the patent).

3. Sandoz's ANDA products do not infringe the asserted claims of the '007 patent

Based on the entirety of the record, including the Court's evaluation of the credibility of the witnesses, the Court finds that UTC has failed to prove by a preponderance of the evidence that Sandoz's label instructs physicians to prescribe Sterile Diluent for Flolan for use with its ANDA products. Therefore, UTC has failed to prove that Sandoz's ANDA products infringe the asserted claims of the '007 patent.

Infringement of the '117 Patent

United Therapeutics alleges that Sandoz's ANDA product directly infringes the '117 patent under the doctrine of equivalents. Sandoz contends that its ANDA products contain treprostinil made through a process that includes intermediates substantially different than those claimed in the '117 patent. For the reasons stated below, the Court finds that UTC has proved by a preponderance of the evidence that Sandoz's ANDA product directly infringes the '117 patent under the doctrine of equivalents.

1. Infringement by Equivalents Legal Standard

The doctrine of equivalents prohibits one from "avoiding infringement liability by making only 'insubstantial changes and substitutions . . . which, though adding nothing, would be enough to take the copied matter outside the claim, and hence outside the reach of law." *Siemens Medical Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011) (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607, 70 S. Ct. 854, 94 L. Ed. 1097, 1950 Dec. Comm'r Pat. 597 (1950)). The doctrine has evolved to protect patentees "against efforts of copyists to evade liability for infringement by making only insubstantial changes to a patented invention." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Corp.*, 535 U.S. 722, 727, 122 S. Ct. 1831, 152 L. Ed. 2d 944 (2002). To this end, infringement may also be established under the doctrine of equivalents because the "scope of a patent is not limited to its

literal terms but instead embraces all equivalents to the claims described." *Id. at 732*. Thus, a product or process that "does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The doctrine of equivalents must be applied to the "individual elements of the claim, not to the invention as a whole." *Id. at 29*.

2. Narrow Claiming

Sandoz argues that UTC is precluded from asserting the doctrine of equivalents because it narrowly claimed the claim element at issue. Sandoz argues that the Federal Circuit has held that a patentee who narrowly describes and claims an invention is not entitled to rely on the doctrine of equivalents to expand the scope of claims that could have been drafted more broadly, but intentionally were left narrow in scope. Specifically Sandoz contends that "the evidence showed that UTC defined the "X" substituent in the '117 patent narrowly with a limited number of specifically defined possible groups, while it defined the "R1" substituent broadly as an "alcohol protecting group," a large genus of potential groups. (Sandoz FF 343-47). Because UTC elected to define "X" narrowly while defining the "R₁" substituent broadly, UTC is precluded from expanding the scope of the claims through use of the doctrine of equivalents."

UTC maintains that Sandoz's "argument misapprehends the law and, regardless, is a red herring where $Z(CH_2)_nX$ is not claimed narrowly. The Court agrees with UTC. Despite Sandoz's assertions otherwise, there is no law that, when accurately applied, would prevent application of the doctrine of equivalents based solely on narrow claiming. Indeed, the bulk of caselaw on which Sandoz relies is simply inapplicable because it contemplates a scenario in which a patentee, through its action, consciously excluded and/or deliberately disavowed the subject matter that it was then seeking to capture under the doctrine of equivalents. The Court finds that there is no such "clear and unmistakable surrender of equivalents" to be found in this case, such that UTC should be prevented from asserting the doctrine of equivalents based on narrow

claiming. Furthermore, the Court notes that, even if the narrow claiming doctrine as described by Sandoz did exist, it would be inapplicable here, as $Z(CH_2)_nX$ is *not* narrowly claimed, embracing *at least* 436 distinct chemical entities. (Tr. 971:15–23 (Williams), May 13, 2014.)¹³ In fact, even when both Z and n are not considered, there are 109 structures within the scope of the X limitation alone. (Tr. 971:24-972:7 (Williams), May 13, 2014.) Based on these facts, the Court finds that a person of ordinary skill in the art would not “believe that United Therapeutics had claimed the X part of claim 1 [of the ’117 patent] narrowly.” (Tr. 972:25-973:9 (Williams), May 13, 2014.)

Thus, the scope of $Z(CH_2)_nX$ does not prevent Sandoz’s PMB group from being embraced as an equivalent.

Direct Infringement By Equivalent

As previously noted, to prove direct infringement under the doctrine of equivalents, a patentee must demonstrate that “the accused device contains an equivalent for each limitation not literally satisfied.” *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 812 (Fed. Cir. 2002).

“An element of an accused [product] is equivalent to an element of the patented invention if the differences between them are insubstantial.” *Martek Biosciences Corp. v. Nutrinova, Inc.*, 520 F. Supp. 2d 537, 547 (D. Del. 2007) (quoting *Warner-Jenkinson*, 520 U.S. at 39). Simply put, the accused product infringes under the doctrine of equivalents “if the element in the accused device performs substantially the same function in substantially the same way to obtain the same result as the claim limitation.” *Id.* at 547-48. Regardless of whether the insubstantial differences or the function test is used, the patentee must provide “particularized testimony and linking

¹³ Under these limitations where Z is limited to oxygen and n is limited to straight chain alkyls of six carbons or less, claim 1 of the ’117 patent defines the “ $(CH_2)_nX$ ” moiety such that that substituent group can represent any one of “436 distinct chemical entities.” (Tr. 971:15-23 (Williams), May 13, 2014.)

Dr. Buchwald agreed that each of the structures proposed by Dr. Williams were within the scope of the “ $(CH_2)_nX$ ” limitation and even that most would not be protecting groups. (Tr. 1403:12-18 (Buchwald), May 15, 2014.)

argument" for each limitation invoking the doctrine of equivalents. *See Texas Instruments v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567 (Fed. Cir. 1996).

Sandoz argues that "the undisputed evidence at trial showed that Alphora's process was not equivalent to the '117 patent process *at least* with respect to steps outside the Pauson-Khand cyclization step." (FF 350, 362-66, 368-73, 380-81). Specifically, Sandoz argues that "the evidence showed that Alphora intentionally designed around the '117 patent, and that their use of the PMB group permitted Alphora to skip the separate deprotection step that involved the creation of substantial quantities of toxic by-products that is required in the '117 patent process." (FF 350, 368-71). Finally, Sandoz argues that "the use of the PMB group also makes it easier for Alphora to purify and characterize its intermediates." (FF 372).

The Process

On December 1, 2011, Sandoz submitted Drug Master File No. 25548 ("DMF"), supplied by Alphora Research Inc. ("Alphora"), for treprostinil sodium.¹⁴ (Tr. 884:14-25 (Williams), May 12, 2014; PTX 333 at Sandoz-Trep 0008367.) Alphora's DMF contains the chemistry, manufacturing and control information for the synthesis and manufacturing of the treprostinil sodium and treprostinil used in Sandoz's ANDA Products as well as each intermediate in the synthesis. (Tr. 974:21-975:11 (Williams), May 13, 2014; PTX-250 at Sandoz-Trep0000278-279; PTX-333 at Sandoz-Trep0008422-8448.)

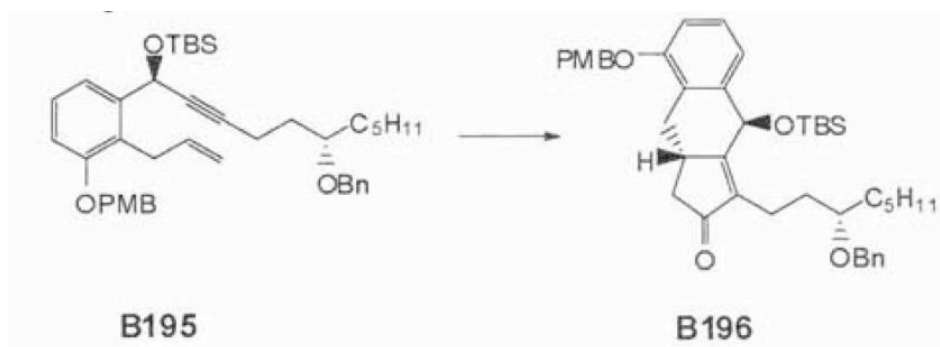
Treprostinil sodium is the active pharmaceutical ingredient of the generic Treprostinil Injection that is the subject of Sandoz's ANDA. (PTX-250; PTX-333; Agreed Fact No. 69, [Proposed] Final Pretrial Order, Ex. 1 (Stipulated Facts) [D.I. 179-1].) Sandoz's ANDA products contain Alphora's treprostinil sodium product, (Tr. 885:10-15 (Williams), May 12, 2014; PTX-250 at Sandoz-Trep0000278-279; PTX-333 at Sandoz-Trep0008422-8448.), and if Sandoz's ANDA is approved, Alphora will supply Sandoz with treprostinil sodium for formulation in Sandoz's ANDA Product. (Tr. 2202:22-25 (Oudenes), May 27, 2014; PTX-250.) Sandoz's ANDA provides an overview of the synthetic process used in creating Sandoz's treprostinil

¹⁴ Alphora also provided Sandoz with a Letter of Authorization to submit in Sandoz's ANDA to allow the FDA to review information in Alphora's DMF in support of Sandoz's ANDA. (Tr. 974:2-17 (Williams), May 13, 2014; PTX-250; PTX-333 at Sandoz-Trep0008371.)

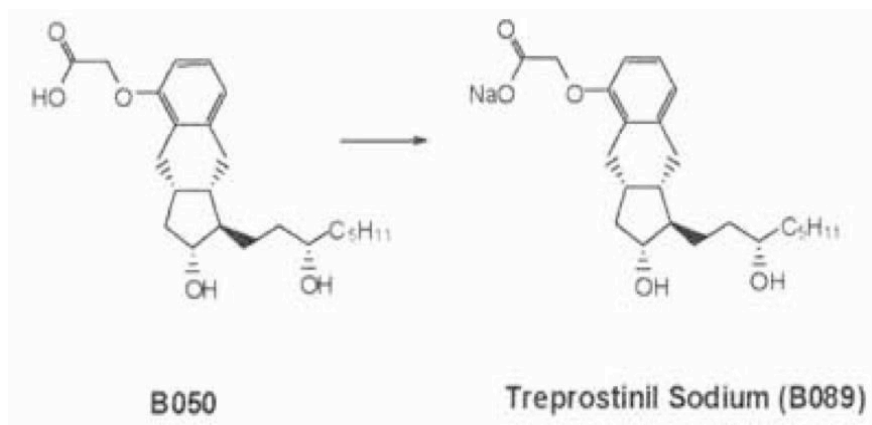
sodium and the same overview (with more detail) is also found in Alphora's DMF. (Tr. 974:21-975:11 (Williams), May 13, 2014; PTX-250 at Sandoz-Trep0000278-279; PTX-333 at Sandoz-Trep0008422-8448.)

A "key step" in both Alphora's synthesis of treprostinil and the route claimed in the '117 patent is the Pauson-Khand reaction. (Tr. 2087:6-15 (McGowan), May 22, 2014.) The route for synthesizing treprostinil claimed in the '117 patent is practical both because it is a "shorter route than other routes" and because the Pauson-Khand cyclization step is stereoselective. (Tr. 2051:9-16 (Gorin), May 22, 2014.) Alphora did not "identify any stereoselective synthetic routes for treprostinil that did not include a Pauson-Khand cyclization." (Tr. 2059:15-18 (Gorin), May 22, 2014.) Synthesis of treprostinil using the Pauson-Khand cyclization is also advantageous because it allows formation of the "tricyclic core of the molecule of treprostinil in one single step while other synthetic routes build [a] tricyclic core over several consecutive steps." (Tr. 2050:14-2051:8 (Gorin), May 22, 2014.)

In developing treprostinil API for Sandoz, Alphora identified the Pauson-Khand cyclization reaction as part of the "preferred route" of synthesis. (Tr. 2085:6-25 (McGowan), May 22, 2014; PTX-39.) Alphora's synthesis of treprostinil sodium includes multiple reaction steps. Alphora's DMF and Sandoz's ANDA refer to the chemical intermediates and products included in that synthesis by code numbers, including B195, B196, B087, B050, and B089. (Tr. 913:8-21 (Williams), May 12, 2014; PTX-250 at Sandoz-Trep0000278-279; PTX-333 at Sandoz-Trep0008433.) In Alphora's synthetic process, the reaction going from B195 to B196, shown below, is a Pauson-Khand reaction. (Tr. 2110:8-18 (McGowan), May 22, 2014; PTX-333 at Sandoz-Trep0008433.)



The Alphora process and the process of the '117 patent both use “the same reagent,” dicobalt octacarbonyl, to carry out the Pauson-Khand step. (Tr. 2120:1-10 (McGowan), May 22, 2014.) Alphora’s synthesis culminates in the synthesis of treprostinil B050, which Alphora converts to treprostinil sodium B089. (Tr. 894:13-895:5 (Williams) May 12, 2014; PTX-250 at



Sandoz-Trep000279; PTX-333 at Sandoz-Trep008441.) Compound “B089 as manufactured by Alphora ha[s] the same structure as reactive treprostinil sodium in Remodulin,” which is made by the process claimed in the '117 patent. (Tr. 2117:13-22 (McGowan), May 22, 2014.)

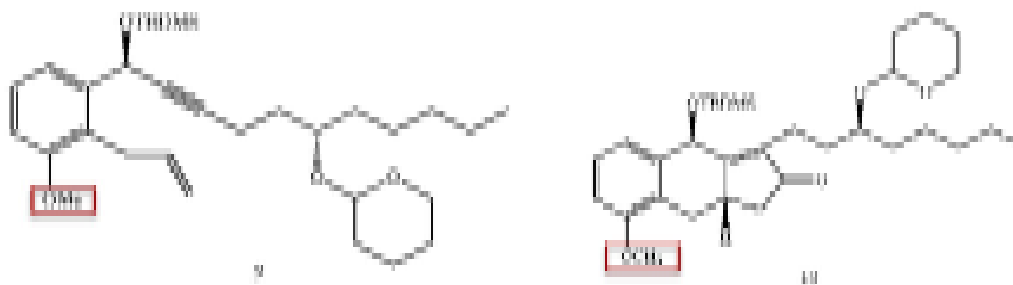
Claim Limitations Present Under the Doctrine of Equivalents

The only claim limitation that Sandoz disputes for the purpose of infringement of the claims of the '117 patent is the use of a para-methoxybenzyl (PMB) group at the $(CH_2)_nX$ substituent on the phenyl ring of the claimed enyne structure and cyclized intermediate present in each of the asserted claims that is used in the process to make Sandoz's ANDA Product. (Tr. 1378:11-1379:5 (Buchwald), May 15, 2014; Tr. 915:14-22 (Williams), May 12, 2014.)

a) Independent Claim 1

The '117 patent specification includes in Example 1 an embodiment of the claims that demonstrates the use of the Pauson-Khand intramolecular cyclization reaction performed with a substituent on the phenyl ring that is within the list of groups $(CH_2)_nX$ defined in each the claims of the '117 patent. (Tr. 916:6-12, 917:9-15, 918:11-22 (Williams), May 12, 2014; PTX-2 at 16:53-17:55.)

Alphora admits that the Alphora process uses "the same reagent" dicobalt octacarbonyl, to carry out the "Alphora equivalent" to the Pauson-Khand step claimed in the '117 patent. (Tr. 2120:1-10 (McGowan), May 22, 2014.) Specifically, as described in the '117 patent specification Example 1, the Pauson-Khand cyclization of enyne 9 to tricyclic intermediate 10 includes a methoxy substituent on the phenyl ring, where $(CH_2)_nX = CH_3$ (methyl).¹⁵

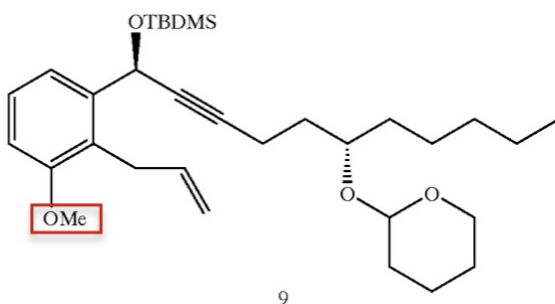


¹⁵ In performing his analysis, Dr. Williams also analyzed other exemplary protecting groups that are defined within the scope of the claims of the '117 patent other than the methyl group and reached the same conclusions. (Tr. 917:16-918:3 (Williams), May 12, 2014; PTX-2.)

(Tr. 917:9-15 (Williams), May 12, 2014; PTX-2 at 16:53-17:55.) Dr. Williams analyzed the entire scope of the claims to perform his analysis. (Tr. 56:18-57:19 (Williams), May 1, 2014; Tr. 873:19-874:18 (Williams), May 12, 2014.) In performing his analysis, Dr. Williams also analyzed other exemplary protecting groups that are defined within the scope of the claims of the '117 patent other than the methyl group and reached the same conclusions. (Tr. 917:16-918:3 (Williams), May 12, 2014; PTX-2.)

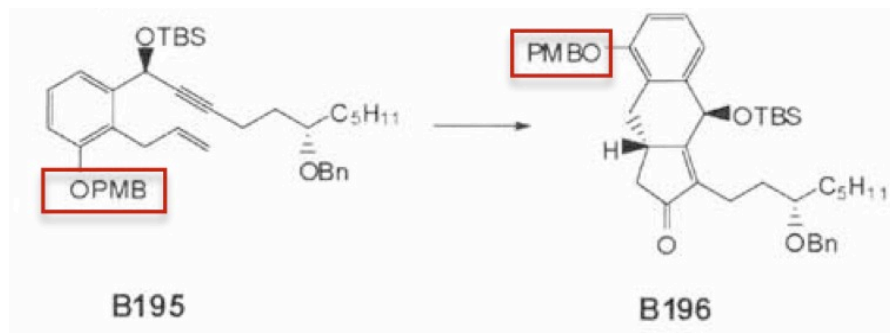
The PMB Group Performs Substantially the Same Function as the Claimed (CH₂)_nX Limitation

The oxygen where the methyl group is attached in Example 1 of the '117 patent (as shown in the box below) to the enyne and cyclized intermediate and where the PMB group is attached to the enyne and cyclized intermediate is a special type of alcohol called a phenol. (Tr. 919:6-9 (Williams), May 12, 2014.)



The phenol is connected directly to the aromatic ring and because of that, phenols are much more acidic than other types of alcohols and have chemistry that is distinct from other types of alcohols. See (Tr. 919:10-20 (Williams), May 12, 2014.) The CH₃ protecting group on the phenol does not undergo any chemical transformation during the Pauson-Khand intramolecular cyclization reaction. (Tr. 920:16-921:5 (Williams), May 12, 2014; PTX-2.) During the Pauson-Khand enyne cyclization step of Alphora's synthesis, converting B195 to B196, the PMB protecting group does not undergo any chemical transformation either, as shown in the drawings

below.



(Tr. 918:25-919:5, 920:9-15 (Williams), May 12, 2014; PTX-333, PTX-250 at Sandoz-Trep 0000278.) Thus, neither the methyl group used in Example 1 of the '117 patent, nor the PMB group used in Alphora's synthesis are participating in the reaction. Consequently, they serve exactly the same function. (Tr. 920:21-921:5 (Williams), May 12, 2014.)

A person of skill in the art would recognize from the literature that a phenol on a substrate used for the Pauson-Khand reaction would need to be protected during the reaction. (Tr. 921:6-11, 922:19-923:9, 924:15-925:5 (Williams), May 12, 2014; PTX-1027 at UTC-Sand-Rem01173159; PTX-1034 at UTC-Sand-Rem01171461.) Protecting groups are very commonly utilized in chemistry and are temporarily installed on a molecule so that a reaction can take place elsewhere on the molecular structure. They are then removed from the molecule, under defined reaction conditions, after they have served their protecting, blocking, or masking functions. For this reason, protecting groups are not typically present in the final chemical product, but are usually removed once their job is done. (Tr. 906:10-25 (Williams), May 12, 2014.)

Alphora admits that PMB is a "protecting group for alcohols," specifically for an "aromatic alcohol," which is "also known as a phenol." It is conventional for persons of ordinary skill in the art, including the chemists at Alphora, to refer to PMB as a protecting group. (Tr. 2034:8-14, 2035:14-18, 2036:15-2037:1 (Gorin), May 22, 2014.) Alcohol protecting groups serve to preserve alcohol functional groups and "enable chemical conversions that may be affected by hydroxyl group[s]." (Tr. 2034:23-12 (Gorin), May 22, 2014.)

The reference "Catalytic Version of the Intramolecular Pauson-Khand Reaction" shows

that during a Pauson-Khand reaction using the same dicobalt octacarbonyl reagent used in both Example 1 of the '117 patent and in Alphora's process, even traces of phenol can create a problem in the reaction. This fact demonstrates that phenol is, in fact, reactive during the Pauson-Khand reaction. (Tr. 923:13-925:5 (Williams), May 12, 2014; PTX-1027 at UTC-Sand-Rem01173159.) Likewise, in the reference "New Promoters For Molybdenum Hexacarbonyl Mediated Pauson-Khand Reaction", certain additives to the Pauson-Khand reaction are explored to examine their effect during the reaction. They found that the addition of phenol as an additive resulted in zero percent of the desired product. This fact provides further evidence that phenols must be protected during the Pauson-Khand reaction. (Tr. 921:6-923:12 (Williams), May 12, 2014; PTX-1034 at UTC-Sand-Rem01171461.)

Here, the phenolic oxygen needs to be protected during the intramolecular cyclization step, from reacting under the Pauson-Khand reaction conditions, and the methyl group described in Example 1 performs that function. (Tr. 921:6-11, 922:19-923:9, 924:15-925:5 (Williams), May 12, 2014; PTX-1027 at UTC-Sand-Rem01171359; PTX-1034 at UTC-Sand-Rem01171461.) In Alphora's synthesis of treprostnil, the PMB group on the B195¹⁶ and B196 structures acts as its protecting group during the Pauson-Khand intramolecular cyclization step. Specifically, in Alphora's synthesis of treprostnil, "PMB is a phenolic protecting group" which is attached to an aromatic alcohol during the Pauson-Khand reaction. (Tr. 919:21-920:15 (Williams), May 12, 2014; Tr. 2039:4-20, 2045:9-11 (Gorin), May 22, 2014; Tr. 2107:8-10 (McGowan), May 22, 2014.)

Alphora has characterized their use of the PMB group only as a protecting group. Alphora's own patent applications not only identify the group on the phenolic oxygen specifically as a protecting group during the Pauson-Khand step used by Alphora to make treprostnil and treprostnil sodium. (Tr. 925:6-9, 926:9-927:10 (Williams), May 12, 2014); PTX-1038 at UTC-Sand-Rem01171509, 516.) But, Alphora has also stated that it is not "aware of any experimental evidence that would show that the PMB group does not serve as a protecting group" during the Pauson-Khand reaction. (Tr. 2034:8-12, 2035:14-18, 2035:21-2036:5, 2036:12-2037:10,

¹⁶ Compound B195 from Alphora's process is "equivalent to" Compound 29 depicted in the Moriarty 2004 JOC arti-

2037:17-2039:20, 2041:15-19 (Gorin), May 22, 2014; Tr. at 2107:8-2122:13 (McGowan), May 22, 2014; Tr. 2193:16-22, 2196:23-2197:8 (Oudenes), May 27, 2014; DTX-171.) Admittedly, Sandoz's expert, Dr. Buchwald, has done no experimental work himself and knows of no experimental data that would "establish that an unprotected phenol ... would actually successfully proceed in a Pauson-Khand reaction." (Tr. 1396:12-1397:12 (Buchwald), May 15, 2014.)

Alphora did not identify any differences between the use of a methyl protecting group used in Example 1 of the '117 patent and the PMB protecting group during the Pauson-Khand reaction. Indeed, Alphora is not "aware of any evidence that the methyl protecting group on the phenolic oxygen functions differently from the PMB group on the phenolic oxygen during the Pauson-Khand reaction." (Tr. 2087:17-2088:5, 2096:6-10, 2113:21-17 (McGowan), May 22, 2014; Tr. 2041:21-2042:22, 2043:23-2044:22 (Gorin), May 22, 2014; Tr. at 2200:17-23, 2202:1-15 (Oudenes), May 27, 2014; PTX-18; PTX-21.) In fact, the Court notes that Dr. Buchwald seemingly conceded to the fact that the PMB group and the methyl group perform the same function when he testified that summarily that either both are doing nothing in the reaction or both are acting as protecting groups. (Tr. 1394:21-1396:11 (Buchwald) May 15, 2014.)

In light of the foregoing facts the Court finds that because neither the methyl protecting group nor the PMB protecting group are participating in the Pauson-Khand reaction, and because both groups function to prevent interference of the phenolic oxygen during that step, both substituents can be said to serve the same function.

*The PMB Group Performs Substantially the Same Way as the Claimed
(CH₂)_nX Limitation*

Example 1 of the '117 patent identifies certain reaction conditions and reagents for use during the enyne intramolecular cyclization step required by each of the claims of the '117 patent. (Tr. 927:24-928:4 (Williams), May 12, 2014; PTX-2 at 17:34-55.) Step 2 of Alphora's synthesis of the treprostinil sodium used for Sandoz's ANDA Product identified in Alphora's DMF also identifies certain reaction conditions and reagents for use during the enyne cyclization step going

cle. (Tr. 2119:17-24 (McGowan), May 22, 2014; DTX-171.)

from B195 to B196. (Tr. 928:5-19, 929:5-933:30 (Williams), May 12, 2014; PTX-333 at Sandoz-Trep0008435.) Both Example 1 of the '117 patent and Alphora's synthesis of treprostinil sodium used for Sandoz's ANDA Product use the exact same $\text{Co}_2(\text{CO})_8$ reagent to perform the intramolecular cyclization step in the exact same ratio of 1.2 to 1 of $\text{Co}_2(\text{CO})_8$ reagent to starting material enyne. (Tr. 929:19-930:17 (Williams), May 12, 2014; PTX-2 at 17:34-55; PTX-333 at Sandoz-Trep0008435.)

Both Example 1 of the '117 patent and Alphora's synthesis of treprostinil sodium used for Sandoz's ANDA Product use the exact same solvent CH_2Cl_2 with stirring at room temperature to perform the intramolecular cyclization step and both are also then distilled and dissolved again in CH_3CN . (Tr. 930:19-931:1, 931:25-932:18 (Williams), May 12, 2014; PTX-2 at 17:34-55; PTX-333 at Sandoz-Trep0008435.) The difference in stirring time was due to the difference in batch size – the scale of the reaction in Alphora's DMF was much larger than the scale of the batch described in the '117 patent and needed more time because of the size and is therefore not a difference. (Tr. 931:2-22 (Williams), May 12, 2014.) Both Example 1 of the '117 patent and Alphora's synthesis of treprostinil sodium used for Sandoz's ANDA Product were then both heated and purified. (Tr. 932:19-933:13 (Williams), May 12, 2014; PTX-2 at 17:34-55; PTX-333 at Sandoz-Trep0008435.)

The Court notes that Dr. Buchwald does not disagree with Dr. Williams' analysis that the same solvents, the same reagents and reaction conditions are used for both the PMB group in the process to make Sandoz's ANDA Product and the methyl group from Example 1 of the '117 patent. (Tr. 1393:3-14, 1393:18-25, 1394:1-11 (Buchwald), May 15, 2014.). Because neither the methyl protecting group nor the PMB protecting group are chemically transformed during the Pauson-Khand reaction, they each perform in substantially the same way. (Tr. 920:9-11, 933:14-20 (Williams), May 12, 2014.)

In light of the foregoing facts, the Court finds that the PMB protecting group and the methyl protecting group perform in substantially the same way because the reagents, solvents, and reaction conditions of the Pauson-Khand reactions in Alphora's synthesis and in the '117 patent are not only substantially similar, but nearly identical. (Tr. 927:22-933:20 (Williams),

May 12, 2014; Tr. 1393:11-21 (Buchwald), May 15, 2014; PTX-2 at 17:34-55; PTX-333 at Sandoz-Trep0008435).

*The PMB Group Has Substantially the Same Result as the Claimed
(CH₂)_nX Limitation*

United Therapeutics' New Drug Application ("NDA") 21-272 discloses the synthetic route and manufacturing details of UTC's Remodulin product. (Tr. 517:19-518:3 (Zaccardelli), May 8, 2014; PTX-894; PTX-521.) Based on the following facts, as established at trial by Plaintiff's expert Dr. Williams, the Court finds that the Remodulin product produced by United Therapeutics is an embodiment of the '117 patent invention. (Tr. 1982:3-13 (Williams), May 22, 2014.)

Both UTC's ANDA and Alphora's DMF disclose substantially similar yields from the intramolecular cyclization step because both are on a similar scale and have a good range of yields greater than 59% for each. (Tr. 962:6-963:8 (Williams), May 13, 2014; PTX-333 at Sandoz-Trep0008435; PTX-523 at UTC-Sand-Rem00026061.)

The methyl and PMB protecting groups each also yield substantially the same result: a successful and scalable Pauson-Khand reaction. Whether methyl or PMB is used, the result is a successfully ring-closed tricyclic product with a protected phenol functional group. (Tr. 961:19-962:11, 962:15-17, 963:9-12 (Williams), May 13, 2014.)

The differences between the (CH₂)_nX group as defined by claims 1-4 of the '117 patent and the PMB group utilized by Alphora and Sandoz for Sandoz's ANDA Product are insubstantial. (Tr. 915:14-22 (Williams), May 12, 2014.) In fact, the PMB group and the methyl group both act protection (similar to masking tape when painting a door) and the difference in structure is no more significant than if the masking tape were a different color. (Tr. 963:16-964:13 (Williams), May 13, 2014.)

The PMB group used by Alphora's process for making Sandoz's treprostinil product is equivalent to the "X" group in claims 1-4 of the '117 patent. (Tr. 910:22-911:2 (Williams), May 13, 2014.) Alphora is not "aware of any differences in the result of the Pauson-Khand reaction

based on whether the phenolic oxygen is protected by a methyl group or a PMB group.” (Tr. 2044:12-22 (Gorin), May 22, 2014.)

In light of the foregoing facts,, the Court finds that the PMB group used by Alphora’s process for making Sandoz’s treprostinil product performs substantially the same function, in substantially the same way, with substantially the same result as the group $(CH_2)_nX$ defined in claims 1-4 of the ‘117 patent. (Tr. 915:14-22 (Williams), May 12, 2014; Tr. 1393:11-21, 1395:16-1396:11 (Buchwald), May 15, 2014.)

Claim Limitations Literally Present

Other than the PMB group discussed above, all limitations of claim 1 are literally met by Alphora and Sandoz’s synthesis of treprostinil and treprostinil sodium. (Tr. 914:23-915:8 (Williams), May 12, 2014; Tr. 966:22-968:18 (Williams), May 13, 2014; Tr. 1378:11-23 (Buchwald), May 15, 2014; PTX-250; PTX-333.)

Conclusion

In light of the foregoing facts and findings, the Court concludes that Sandoz’s ANDA product will directly infringe the asserted claims of the ‘117 patent under the doctrine of equivalents.¹⁷

III. VALIDITY

Sandoz contends that both the ‘007 and ‘117 *patents* are invalid as anticipated and obvious. Sandoz further asserts the ‘007 *patent* is invalid as its claims are indefinite. The Court addresses

¹⁷ UTC asserts Sandoz will induce Alphora to infringe the ‘117 patent by making and using treprostinil using the process covered by the ‘117 patent claims. Sandoz, however, argues that Alphora would manufacture treprostinil at its facilities located in Canada, subsequently sell it to Sandoz Canada, which would then formulate the final dosage form in its facilities in Canada. (FF 382-85). Thus, all of Alphora’s conduct that UTC alleges constitutes direct infringement of the ‘117 patent will occur outside the United States. Alphora’s activities cannot constitute direct infringement because the U.S. patent laws do not reach Alphora’s conduct in Canada.

The Court is not convinced by the evidence before it that Sandoz Canada and Sandoz USA should not, in fact, be treated as one entity. To the extent that they are so closely intertwined in their manufacturing and sales processes, the Court believes Sandoz’s argument is no more than a weak attempt to avoid induced infringement liability.

each asserted basis for invalidity below.

A. Legal Standards

An issued patent is presumed to be valid. *See 35 U.S.C. § 282*. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (obviousness); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (written description). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted).

1. Anticipation Standard

"[I]nvalidity by anticipation requires that the four corners of a single[] prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). The elements of the prior art must be arranged or combined in the same manner as in the claim at issue, but the reference need not satisfy an *ipsissimis verbis* test¹⁸. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citations omitted). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Id.* (internal citations omitted).

The Federal Circuit recently discussed the standards for inherent disclosure in *Verizon Services Corp. v. Cox Fibernet Virginia, Inc.*, 602 F.3d 1325 (Fed. Cir. 2010):

"[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." However, a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under *section 102*, however, differs from the enablement standard under *section 112*." It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under *section 102*.

Id. at 1337 (internal citations omitted). In sum, inherent anticipation "requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Labs, Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (quoting *Hansgirk v. Kemmer*, 102 F.2d 212, 214, 26 C.C.P.A. 937, 1939 Dec. Comm'r Pat. 327 (C.C.P.A. 1939)). To be inherent, an undisclosed feature must "necessarily and inevitably" flow from practice of what is disclosed. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003).

Therefore, if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate. See *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (finding no inherent anticipation where testing evidence demonstrated that the prior art example could yield crystals of either the claimed polymorph or a different polymorph). Whether a prior art reference anticipates a patent claim is a question of fact and must be proven by clear and convincing evidence.⁵ See

¹⁸ i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Advanced Display Sys., 212 F.3d at 1281.

2. Obviousness Standard

A patent may be invalidated if the subject matter of the patent is obvious. A patent may not be obtained "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007)(quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933, 184 L. Ed. 2d 725 (U.S. 2013) (citing *Procter & Gamble*, 566 F.3d at 994); *see also Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.").

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 418; *see also Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Instead, proof of obviousness requires proof that a person of ordinary skill in the art "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994 (quoting *Pfizer*, 480 F.3d at 1361); *see also Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009). Such a person would interpret prior art references "using common sense

and appropriate perspective." *Unigene Labs.*, 655 F.3d at 1361.

While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007). In addition, the use of hindsight is not permitted when determining whether a claim would have been obvious to one of ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning").

"[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).

3. Indefiniteness Standard

Every patent's specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 ¶ 2. In the recent U.S. Supreme Court case of *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369, 2014 WL 2440536 (U.S. June 2, 2014), the Court held that such claims must, when "viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Id.* at 7 (rejecting prior Federal Circuit precedent that formulated the indefiniteness standard as an inquiry into whether such claims were "not amenable to construction or insolubly ambiguous"). In so holding, the Court stated that "[i]t cannot be sufficient that a court can ascribe *some* meaning to a patent's claims; the definiteness inquiry trains on the understanding of a skilled artisan at the time of the patent application, not that of a court viewing matters *post hoc*." *Id.* at 18; *see also Nautilus, Inc. v. Biosig Instruments, Inc.*, 715 F.3d 891, 898 (Fed Cir. 2013), *vacated on other grounds* 13-369, 2014 WL 2440546 (U.S. June 2, 2014) ("[I]f reasonable efforts at claim construction result in a definition that does not provide sufficient particularity and clarity to inform skilled artisans of the bounds of the claim, the claim is insolubly ambiguous and invalid for indefiniteness"). While this standard takes into account "the inherent limitations of language," it requires every "patent . . . [to] be precise enough

to afford clear notice of what is claimed, thereby “apprising the public of what is still open to them.” *Nautilus*, 2014 WL 2440536, at 7 (quoting *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996)).

Importantly, this new standard does not disrupt three key aspects of the § 112, ¶ 2 inquiry: “First, definiteness is to be evaluated from the perspective of someone skilled in the relevant art.” *Nautilus*, 2014 WL 2440536, at 6 (citing *General Elec. Co v. Wabash Appliance Corp.*, 304 U.S. 364, 371 (1938)). “Second, in assessing definiteness, claims are to be read in light of the patent’s specification and prosecution history.” *Nautilus*, 2014 WL 2440536, at 6 (citing *United States v. Adams*, 383 U.S. 39, 48–49 (1966); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 741 (2002)). “Third, definiteness is measured from the viewpoint of a person skilled in the art *at the time the patent was filed.*” *Nautilus*, 2014 WL 2440536, at 6.

B. Validity of the ’007 Patent

1. Scope and Content of the Prior Art

a. European Patent Application No. 0 347 243 A1 (PTX-316)

Sandoz has identified only one prior art reference that it contends anticipates any of the Asserted Claims of the ’007 patent: European Patent Application No. 0 347 243 A1 (“EP ’243”). (Tr. 646:15-647:2 (Miller), May 9, 2014; Tr. 1589:1-9 (Thomson), May 16, 2014.) EP ’243 published on December 20, 1989 and is entitled “Prostaglandin analogues for use in medicine.” (PTX-316 at Sandoz-Trep 0006966.) Sandoz expert Dr. Thomson relies primarily on Example 1 of EP ’243 for his opinion that EP ’243 invalidates the Asserted Claims of the ’007 patent. (Tr. 647:24-648:4 (Miller), 9, 2014; Tr. 1511:8-13, 1516:4-9 (Thomson), May 15, 2014.)

EP ’243 Example 1 discloses animal test models for a pharmacological proof of concept study. (Tr. 648:5-9; 650:9-13 (Miller), May 9, 2014; Tr. 1490:18-1492:2 (Thomson), May 15, 2014; PTX-316 at Sandoz-Trep 0006971.) EP ’243 Example 1 describes experiments with “solutions [of a] test compound [that] were successively administered to each of four animals by i.v. infusion ...” (PTX-316 at Sandoz-Trep 0006971; Tr. 648:5-9 (Miller), May 9, 2014; Tr. 1492:3-11 (Thomson), May 15, 2014.) The “test compound” of EP ’243 Example 1 is treprostinil.

(Tr. 651:14-20 (Miller), May 9, 2014; Tr. 1492:18-21 (Thomson), May 15, 2014.) As this single-day experiment was done with “an open-chest model,...it would be understood by a skilled artisan that the cats would be killed at the end of the experiment.” (Tr. 649:5-12 (Miller), May 9, 2014.)

The researchers behind EP '243 “were trying to determine if the test compound disclosed in EP '243 had any type of pharmacological effect on [a] simulated condition of PAH” and were not “concerned about bloodstream infections” because, as Dr. Miller explained, the EP '243 experiment was “an experiment that occurred over a very short period of time, two hours” such that “it was understood that the cats at the end of this open-chest model would have been euthanized or killed at the end of that time period,” which means there was “not enough time to be able to track or trend bloodstream infections” and that there wasn’t anywhere near “the type of exposure times that patients would have with, for example, the administration of Remodulin where bloodstream infections have been tracked.” (Tr. 650:9-651:1 (Miller), May 9, 2014.)

EP '243 “never mentions bacteria,” “bacteremia,” “bloodstream infections” or “sepsis.” (Tr. 1583:17-24 (Thomson), May 16, 2014.) EP '243 “never mentions the potential antimicrobial properties of any particular diluent.” (Tr. 1584:1-3 (Thomson), May 16, 2014.) EP '243 “never mentions any antimicrobial effectiveness testing.” (Tr. 1584:4-6 (Thomson), May 16, 2014.) EP '243 “has no data relating to bacteria or antibacterial testing.” (Tr. 1584:7-9 (Thomson), May 16, 2014.) “EP '243 does not mention, does not disclose or discuss anything about antimicrobial effectiveness or antimicrobial effectiveness testing; there’s no discussion about bacteria, gram positive or gram negative bacteria; there is also no discussion on bloodstream infections, or contamination of blood such as bacteremia or sepsis or anything in that field.” (Tr. 649:24-650:8 (Miller), May 9, 2014.)

b. 2006 Remodulin Package Insert¹⁹ (“Remodulin Insert”) (PTX-264, DTX-148)

The 2006 Remodulin Package Insert is “the package insert that United Therapeutics included with Remodulin prior to the '007 patent.” (Tr. 674:14-16 (Miller), May 9, 2014.) The 2006 Remodulin Package Insert specifies that, for intravenous administration, “**Remodulin must**

¹⁹ The 2006 Remodulin package insert was the package insert disclosed prior to the September 2007 priority date for

be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection and is administered intravenously by continuous infusion ...” (DTX-148 at Sandoz-Trep 0004343 (emphasis original).) This disclosure in the 2006 Remodulin Package Insert specifies that Remodulin “must be diluted with either sterile water for injection or 0.9 percent sodium chloride injection, the latter also being known as saline.” Both of those diluents are “roughly pH neutral.” (Tr. 674:17-25 (Miller), May 9, 2014.) The 2006 Remodulin Package Insert further states that “Diluted Remodulin has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4,000 ng/mL).” (DTX-148 at Sandoz-Trep 0004343.)

The Remodulin Package Insert does not disclose any of the elements missing from EP ’243. (Tr. 1639:19-1640:10 (Thomson), May 16, 2014; *see also* Tr. 656:16-657:7, 678:16-22 (Miller), May 9, 2014.)

c. 1999 Flolan Package Insert (“Flolan Insert”) (PTX-263, DTX-147)

The 1999 Flolan Package Insert sets forth “Product Information” for “FLOLAN® (epoprostenol sodium) for Injection.” (DTX-147 at Sandoz-Trep 0004305.) The 1999 Flolan Package Insert specifies that Flolan must be administered in Sterile Diluent for Flolan. (Tr. 676:9-13 (Miller), May 9, 2014; DTX-147 at Sandoz-Trep 0004305 (“FLOLAN is a white to off-white powder that must be reconstituted with STERILE DILUENT FOR FLOLAN.”).) The 1999 Flolan Package Insert also specifies the chemical composition of Sterile Diluent for Flolan, namely “94 mg glycine, 73.5 mg sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injection, USP.” (DTX-147 at Sandoz-Trep 0004305; Tr. 676:14-20 (Miller), May 9, 2014.) The 1999 Flolan package insert further specifies that “[t]he reconstituted solution of FLOLAN has a pH of 10.2 to 10.8 and is increasingly unstable at lower pH.” (DTX-147 at Sandoz-Trep 0004305.) The 1999 Flolan Package Insert further includes express warnings that Flolan may only be reconstituted in Sterile Diluent for Flolan:

WARNINGS: FLOLAN must be reconstituted only as directed using STERILE DILUENT for FLOLAN. FLOLAN must not be reconstituted or

the application that resulted in the ’007 patent. (Tr. 673:20-674:9, 674:14-16 (Miller), May 9, 2014; DTX-148.)

mixed with any other parenteral medications or solutions prior to or during administration.

(DTX-147 at Sandoz-Trep 0004311 (emphasis original).) The 1999 Flolan package insert includes no mention of treprostinil. (Tr. 677:4-6 (Miller), May 9, 2014.) The Flolan Package Insert does not disclose any of the elements missing from EP '243. (Tr. 1641:6-14, 1641:19-23 (Thomson), May 16, 2014; Tr. 679:1-5 (Miller), May 9, 2014.)

d. The Prior Art as a Whole

“In September of 2007, ... a person of ordinary skill in the art [would not have been] aware of high pH glycine diluents that selectively kill gram negative bacteria” because “the earliest disclosure of that property” was the '007 patent itself. (Tr. 664:12-17 (Miller), May 9, 2014.) As Sandoz’s expert, Dr. Thomson, admitted “none of the prior art identifies the differential effect of killing gram negative bacteria and inhibiting gram positive bacteria as claimed in the '007 patent.” (Tr. 1582:12-15 (Thomson), May 16, 2014.)

2. Anticipation

As previously noted, a patent is invalid as anticipated only if “each and every limitation is found in a single prior art reference.” *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 704 (Fed. Cir. 2012). In other words, the Court must analyze each asserted claim, limitation by limitation, and determine whether each limitation is contained, either expressly or inherently, in a single piece of prior art. In other words, “[a]nticipation ... requires identity of invention: the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate.” *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). If the reference does not expressly disclose a particular limitation, it still may inherently disclose that limitation if the “missing characteristic is *necessarily present*, or inherent, in the single anticipating reference.” *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004) (citation omitted, emphasis added). The

missing characteristic or result, however, “must *inevitably result* from the disclosed steps” in the prior art. *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (emphasis added). “An invitation to investigate is not an inherent disclosure.” *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004). Furthermore, probability, possibility, or capability cannot prove inherent anticipation. *See Motorola Mobility, LLC v. Int’l Trade Comm’n*, 737 F.3d 1345, 1350 (Fed. Cir. 2013).

Sandoz contends that European patent application, EP ’243 (PTX-316), anticipates the ’007 Asserted Claims. However, UTC maintains that Sandoz has failed to prove by clear and convincing evidence that EP ’243 expressly or inherently teaches each and every limitation of the asserted claims or that EP ’243 enables the ’007 patent. Specifically, UTC argues that multiple limitations of the ’007 patent claims are neither expressly disclosed by nor necessarily or inevitably included in EP ’243, including “selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria” and “low buffer capacity.”

For the reasons set forth below, the Court concludes that Sandoz has failed to prove by clear and convincing evidence that EP ’243 anticipates the claims of the ’007 patent.

No Disclosure: EP ’243 does not expressly or inherently teach each and every limitation of the asserted claims of the ’007 patent

i. Independent Claim 1

EP ’243 does not anticipate claim 1 or any of its dependent claims because there is no express or inherent disclosure of the limitations of claim 1 discussed specifically below. (Tr. 658:18-660:18 (Miller), May 9, 2014.)

Claim 1 does not disclose a “pharmaceutical preparation”

A person of ordinary skill in the art would understand that a “pharmaceutical preparation” or “pharmaceutical composition” is something that would be “safe and effective for use.” (Tr. 665:8-15 (Miller), May 9, 2014.) EP ’243 does not expressly or inherently disclose or suggest either a “pharmaceutical preparation” as required by independent claim 1 and claims dependent thereon, or a “pharmaceutical composition” as required by claim 23, because “a skilled artisan

would not consider the test compound in EP '243 to be a pharmaceutical preparation; there's no suggestion that these would be safe and effective for use; and furthermore, EP '243 was testing [a] compound in a cat model that had a simulated condition or symptom of PAH." (Tr. 659:9-23, 665:8-18 (Miller), May 9, 2014.) A person of ordinary skill would not conclude that EP '243 disclosed a pharmaceutical preparation or pharmaceutical composition unless it disclosed the results of "stability testing, compatibility studies, [and] even antimicrobial studies" showing that it was safe and effective for use. (Tr. 666:25-667:4 (Miller), May 9, 2014; PTX-316.) EP '243 does not disclose the results of "any experiments that would inform a person of ordinary skill in the art that its test compound solutions would be suitable pharmaceutical compositions." (Tr. 666:21-24 (Miller), May 9, 2014.) Accordingly, a person of ordinary skill in the art would conclude that the test solutions of EP '243 Example 1 are not necessarily a "pharmaceutical composition" or "pharmaceutical preparation" for use in the prophylaxis, treatment, or diagnosis of pulmonary hypertension, but are instead merely drug substances used to test the efficacy of the compound in an animal study. (Tr. 670:16-671:7 (Miller), May 9, 2014; PTX-316 at Sandoz-Trep 0006971.)

Does not disclose a method of "Selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria"

The Court finds that the administration to cats of the buffer solutions described in EP '243. Example 1 does not inherently meet the limitation "[a] method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria" because: (1) the high pH solutions of EP '243 would not necessarily or inevitably selectively kill gram negative bacteria and (2) testing would be required to determine whether a particular solution within the description of EP '243 Example 1 selectively kills gram negative bacteria.

Sandoz expert Dr. Thomson stated "[t]he entire premise of the '007 patent" is that "high pH glycine buffer systems will kill gram negative bacteria and inhibit the growth of gram positive bacteria." (Tr. 1516:4-17 (Thomson), May 15, 2014.) Sandoz expert Dr. Thomson relies on his interpretation of the '007 patent as supposed evidence that "the buffer solutions of treprostinil, disclosed in Example 1 of EP '243, inherently possess the property of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria." (Tr. 1516:4-1517:3

(Thomson), May 15, 2014.)

However, “[H]igh pH by definition would not necessarily kill or inhibit microorganisms.” (Tr. 1610:19-22 (Thomson), May 16, 2014; PTX-276 at Sandoz-Trep 0004793.) Both parties’ experts agree that “[S]electively killing [or reducing] gram negative bacteria and inhibiting the growth of gram positive bacteria” is not the natural or necessary result of a high pH environment. “[B]acteria would not necessarily die or be killed at a pH of 10 or 11.” (Tr. 1610:19-25, 1611:6-22 (Thomson), May 16, 2014.); “[G]ram negative or gram positive bacteria aren’t inevitably killed or inhibited ... by a pH of 10 or 11.” (Tr. 1608:5-8, 1611:1-5, 1611:23-1612:3 (Thomson), May 16, 2014.) *see also* Tr. 574:10-15 (Miller), May 8, 2014; Tr. 657:22-25 (Miller), May 9, 2014.) Dr. Thompson himself testified that Catalano discloses a more than “hundred-fold increase” of Salmonella at a pH of 10, which “shows that high pH by definition would not necessarily or kill or inhibit microorganisms” and that “bacteria would not necessarily die or be killed at a pH of 10 or 11[.]” (Tr. 1610:1-25 (Thomson), May 16, 2014)

Furthermore, with respect to the test compound used in EP ‘243, a person of ordinary skill in the art would understand that “the buffer solutions in example 1 of EP ’243 could have contained any number of ... materials” other than sodium hydroxide, which is contained in SDF. EP ’243 also “contains no specific description of the concentration of glycine or the amount of glycine used” and thus “discloses [a] potential wide range of glycine for the buffer.” (Tr. 1591:13-23, 1592:13-17, 1593:13-16, 1594:5-8, 1594:12-15 (Thomson), May 16, 2014.) A person of ordinary skill in the art would also know that “out of those infinite number of combinations to make the test compound that is disclosed in EP ’243, it is understood that small changes in those compounds or even the changes in the concentration of the compounds, can result in significant changes in any antimicrobial activity that the compound might have.” (Tr. 651:24-652:12, 657:8-21 (Miller), May 9, 2014.) While “working directly with the drug development group” at Bausch & Lomb, Dr. Miller had “personal experience” modifying a drug formulation by “making very ... small concentration changes in a particular component.” “At one point [Dr. Miller’s group] had very good antimicrobial activity, good kill of bacteria, but as soon as [they] made that change [they] lost all of the antimicrobial activity. And in some cases [they] even saw situations where the

organisms were now growing in -- during the antimicrobial test.” (Tr. 652:13-653:2 (Miller), May 9, 2014.)

“EP ’243 does not include the results of any testing on whether or not the gram negative or gram positive bacteria survive in the solution described in Example 1. ... [T]here’s no testing in EP ’243 of whether or not bacteria survive.” (Tr. 1618:25-1619:7 (Thomson), May 16, 2014.) Therefore, this Court finds that Dr. Thomson’s interpretation of the ’007 patent specification is belied by: (a) the prior art disclosures that gram negative bacteria may survive or grow in high pH environments (Findings of Fact 359-378, *supra*); (b) Dr. Thomson’s admissions that high pH does not necessarily kill or inhibit bacteria (Findings of Fact 402-406, *supra*); and (c) the fact that testing would be required to determine whether any particular buffer solution would selectively kill gram negative bacteria and inhibit the growth of gram positive bacteria (Findings of Fact 407-410, *supra*).²¹

Does not disclose “Low buffer capacity”²²

²¹ ***The Buffer Used in EP ’243 Example 1 Was Not Necessarily or Inevitably SDF***

“[T]he buffers used in example 1 of EP ’243 weren’t necessarily Sterile Diluent for Flolan.” (Tr. 1595:1-8 (Thomson), May 16, 2014; *see also* Tr. 653:7-10, 791:21-792:6 (Miller), May 9, 2014.) “[T]he buffers used in Example 1 of EP ’243 weren’t inevitably Sterile Diluent for Flolan.” (Tr. 1595:5-8 (Thomson), May 16, 2014.) Every 50 mL of SDF contains 94 mg glycine, 73.3 mg sodium chloride, and sodium hydroxide added to adjust the pH. (PTX-003 at 4:46-49.) “[N]othing in EP ’243 Example 1 leads to the conclusion that for every 50 milliliters of the diluent it contained 73.3 milligrams of sodium chloride.” (Tr. 1592:13-17 (Thomson), May 16, 2014.) “[N]othing in EP ’243 Example 1 expressly identifies any amount of sodium hydroxide” and “there’s no expressed reference in the claims [of EP ’243] to sodium hydroxide.” (Tr. 1594:5-11 (Thomson), May 16, 2014.) As one of the inventors for EP ’243 testified, sodium hydroxide is “not suitable for administering to animals” like the cats receiving the test compound in EP ’243. (Tr. 2402:18-25 (Tadepalli), May 27, 2014.) “[T]he buffer solutions in example 1 of EP ’243 could have contained any number of other materials.” (Tr. 1594:12-15 (Thomson), May 16, 2014.) Dr. Thomson’s opinion that EP ’243 used SDF has “no other basis” than “the references that are in the search report” appended to EP ’243. (Tr. 1628:14-21 (Thomson), May 16, 2014.)

The search report was prepared by the patent examiner, not the inventors. (Tr. 789:21-790:8 (Miller), May 9, 2014; PTX-316 at Sandoz-Trep 0006976 (indicating that the “European Search Report” appended to EP ’243 was prepared by patent examiner Mazzucco after EP ’243 was filed).) The ’139 patent is not mentioned or included in EP ’243 or the EP ’243 search report. (Tr. 1629:23-1630:9 (Thomson), May 16, 2014; PTX-316.) EP ’243 only cites Whittle 1984 and Whittle 1985 for the proposition that “[no]n-benzindene prostaglandins having similar properties have also been described.” (PTX-316 at Sandoz-Trep 0006967; Tr. 1632:11-1633:7 (Thomson), May 16, 2014.) None of the specific cites to EP ’768 in the search report “refer to a high pH glycine diluent or SDF.” (Tr. 1635:4-1637:1 (Thomson), May 16, 2014.) “The only thing that’s referenced there [in the search report citations to EP ’768] is water for injection having a pH value of 7.” (Tr. 1637:2-19 (Thomson), May 16, 2014.) EP ’243 “does not” “incorporate by reference or cite any other publication that describes the composition of the test compound solution in example 1.” (Tr. 653:7-10 (Miller), May 9, 2014; PTX-316 at Sandoz-Trep 0006971.)

²² “[B]uffer capacity[] depend[s] on the kind and concentration of the buffer components, the pH region involved and the kind of acid or alkali added.” (Tr. 1624:9-18 (Thomson), May 16, 2014; DTX-175 at 245.) “[L]ow buffer capacity

Sandoz concedes that EP '243 does not expressly disclose the “low buffer capacity” limitation as required by claim 1 of the '007 patent. Sandoz expert Dr. Thomson admitted that EP '243 does not expressly disclose the “low buffer capacity” limitation. (Tr. 1503:23-1504:1 (Thomson), May 15, 2014; Tr. 1596:3-15 (Thomson), May 16, 2014.)

“EP '243 example 1 ... does not disclose enough information to calculate the buffer capacity.” (Tr. 1623:12-15 (Thomson), May 16, 2014.) In light of the highly detrimental testimony of Sandoz's expert, as highlighted below, this Court finds that Sandoz has failed to prove that low buffer capacity is inherently anticipated by EP '243:

- the '007 patent claims requiring low buffer capacity are “not inherently anticipated as [he] understand[s] inherent anticipation.” (Tr. 1596:3-21 (Thomson), May 16, 2014.)
- “[A] person of ordinary skill in the art” would not “be able to have concluded with certainty that the solutions in Example 1 had low buffer capacity” because the “technician could have prepared on a particular day, by error or intent, a high buffer solution.” (Tr. 1511:19-1512:2 (Thomson), May 15, 2014.)
- “[P]arenteral solutions do not necessarily have low buffer capacity.” (Tr. 1621:1-12 (Thomson), May 16, 2014.)
- One could use “a high buffer capacity solution for parenteral administration.” (Tr. 1622:25-1623:4 (Thomson), May 16, 2014.)
- “[T]here are times when low buffer capacity is not feasible.” (Tr. 1620:23-25 (Thomson), May 16, 2014.)
- The solutions in EP '243 Example 1 could have intentionally been prepared with high buffer capacity. (Tr. 1511:19-1512:2 (Thomson), May 15, 2014.)
- EP '243 Example 1 “contains no specific description of the concentration of glycine or the amount of glycine used.” (Tr. 1591:13-23 (Thomson), May 16, 2014.)
- EP '243 discloses “a wide range of glycine for the buffer” of Example 1. (Tr. 1591:21-23 (Thomson), May 16, 2014.)
- “[T]he buffer solutions in example 1 of EP '243 could have contained any number of other materials.” (Tr. 1594:12-15 (Thomson), May 16, 2014.)
- EP '243 Example 1 “does not disclose enough information to calculate buffer capacity.” (Tr. 1623:12-15 (Thomson), May 16, 2014.)
- As Dr. Thomson admitted, “low buffer capacity isn't the only way to control for possible damage from a high pH solution” because “there are other ways depending on route of administration.” (Tr. 1625:5-20 (Thomson), May 16,
- 2014.)

just means there's a small amount of glycine, and it will resist some changes, but not big changes. If you add more glycine it can resist larger changes. So that's -- that's simply the concept of buffer capacity.”

- The rate of infusion “could also be a factor that could help mitigate [the potential damage of high pH.] ... You could use a -- potentially a higher buffer capacity. I wouldn’t say high, you could perhaps get away with it by tinkering with the infusion rate.” (Tr. 1642:7-25 (Thomson), May 16, 2014.)

see generally (Tr. 1504:2-17 (Thomson), May 15, 2014; *see also* Tr. 1591:9-12 (Thomson), May 16, 2014.)

c) Dependent Claims 4 and 5

Claims 4 and 5 of the ’007 patent depend from claim 1 and include all the limitations of claim 1. (PTX-003 at 8:3-6; Tr. 660:3-14 (Miller), May 9, 2014; Tr. 1524:11-19 (Thomson), May 15, 2014.) For the same reasons why EP ’243 does not expressly or inherently disclose or suggest all the limitations required by claim 1, it cannot disclose or suggest all the limitations of dependent claims 4 and 5. (Tr. 660:3-14 (Miller), May 9, 2014.)

d) Dependent Claims 9 and 10

Claims 9 and 10 of the ’007 patent depend from claim 1 and include all the limitations of claim 1. (PTX-003 at 8:15-19, Tr. 660:3-14 (Miller), May 9, 2014; Tr. 1527:6-14 (Thomson), May 15, 2014.) For the same reasons why EP ’243 does not expressly or inherently disclose or suggest all the limitations required by claim 1, it cannot disclose or suggest all the limitations of dependent claims 9 and 10. (Tr. 660:3-14 (Miller), May 9, 2014.)

Dependent claim 9 adds the limitation “injecting the pharmaceutical preparation into a mammal *in need thereof*.” (PTX-003 at 8:15-16)(emphasis added). Dependent claim 10 adds the limitation “wherein the pharmaceutical preparation is injected intravenously into a mammal *in need thereof*.” (PTX-003 at 8:17-19) (emphasis added). EP ’243 does not expressly or inherently disclose or suggest injecting a high pH pharmaceutical preparation “into a mammal in need thereof” as required by claims 9 and 10 of the ’007 patent. (Tr. 665:8-18, 666:3-11 (Miller), May 9, 2014; PTX-316.) In Example 1 of the EP ’243, hypoxia was “induced” in the anesthetized cats “by ventilating with 10% oxygen in nitrogen.” (PTX-316 at Sandoz-Trep 0006971.) The hypoxic condition “was used to simulate a condition of PAH.” (Tr. 648:10-16 (Miller), May 9, 2014.) “It

was this hypoxic condition that induced a symptom of PAH.” (Tr. 648:17-649:4 (Miller), May 9, 2014.) The anesthetized cats did not have pulmonary hypertension, therefore they were not *in need of* treatment for pulmonary hypertension.

e) Dependent Claim 21

Claim 21 of the ‘007 patent depends from claim 1 and includes all the limitations of claim 1. (PTX-003 at 8:49-51; Tr. 660:3-14 (Miller), May 9, 2014.) For the same reasons why EP ’243 does not expressly or inherently disclose or suggest all the limitations required by claim 1, it cannot disclose or suggest all the limitations of dependent claim 21. (Tr. 660:3-14 (Miller), May 9, 2014.) Dependent claim 21 includes the additional limitation “injecting the pharmaceutical preparation into a mammal in need thereof.” (PTX-003 at 8:49-51.) As set forth above, this Court finds that EP ’243 does not expressly or inherently disclose or suggest injecting a high pH pharmaceutical preparation “into a mammal in need thereof,” and thus EP ’243 does not expressly or inherently disclose or suggest this limitation of claim 21.

f) Independent Claim 11

Sandoz’s expert presented no testimony that EP ’243 discloses “a method of reducing the occurrence of bloodstream infections into a mammal being treated with an active agent” as required by claim 11. (Tr. 1530:10-23 (Thomson), May 15, 2014 (offering no testimony pertaining to reducing the occurrence of bloodstream infections).) EP ’243 does not expressly or inherently disclose or suggest “[a] method of reducing the occurrence of blood stream infections into a mammal being treated with an active agent ... wherein the administration reduces the gram negative bacteria and inhibits the growth of gram positive bacteria” as required by claims 11 of the ’007 patent. (Tr. 660:19-662:3 (Miller), May 9, 2014.) As set forth above this Court finds that EP ’243 does not expressly or inherently disclose or suggest “selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria.” For the reasons set forth therein, EP ’243 also does not expressly or inherently disclose or suggest “reduc[ing] the gram negative bacteria and inhibit[ing] the growth of gram positive bacteria” is required by claim 11 of the ’007

patent.

g) Dependent Claim 13

Claim 13 of the '007 patent depends from claim 11 and includes all the limitations of claim 11. (PTX-003 at 8:30-31.) For the same reasons why EP '243 does not expressly or inherently disclose or suggest all the limitations required by claim 11, it cannot disclose or suggest all the limitations of dependent claim 13. (Tr. 662:4-16 (Miller), May 9, 2014.)

h) Dependent Claim 16

Claim 16 of the '007 patent depends from claim 11 and includes all the limitations of claim 11. (PTX-003 at 8:37-38.) For the same reasons why EP '243 does not expressly or inherently disclose or suggest all the limitations required by claim 11, it cannot disclose or suggest all the limitations of dependent claim 16. (Tr. 662:4-16 (Miller), May 9, 2014.)

i) Dependent Claim 17

Claim 17 of the '007 patent depends from claim 11 and includes all the limitations of claim 11. (PTX-003 at 8:39-40.) For the same reasons why EP '243 does not expressly or inherently disclose or suggest all the limitations required by claim 11, it cannot disclose or suggest all the limitations of dependent claim 17. (Tr. 662:4-16 (Miller), May 9, 2014.)

For the reasons state above, the Court concludes that Sandoz has failed to prove that EP '243 expressly or inherently teaches each and every limitation of the asserted claims of the '007 patent.

b. No Enablement: EP 243 Does Not Enable a Skilled Artisan to Practice the (Antimicrobial) Claims of the '007 Patent Without Undue Experimentation

As noted previously, the Federal Circuit has held that a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Verizon Services Corp. v. Cox Fibernet Virginia, Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010).

Therefore, in order “To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate.” *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003) (en banc). “Enablement requires that ‘the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation.’” *Id.* at 1054 (citation omitted).²³ In order to qualifying as an anticipatory reference, EP ’243 must therefore teach one of ordinary skill in the art to make and/or carry out **each of** the claims of the ’007 patent without undue experimentation.²⁴

The test solution used in Example 1 of EP ’243 is described as having “three attributes: [t]he presence of treprostinil; the presence of some amount of glycine; and ... a pH of 10.5.” (Tr. 651:14-20 (Miller), May 9, 2014; *see also* PTX-316 at Sandoz-Trep 0006971.)_As Dr. Miller testified, “[A]n infinite number of solutions” “fall within those parameters.” (Tr. 651:21-23 (Miller), May 9, 2014.) As Sandoz expert Dr. Thomson admitted, this description of the buffer solution in Example 1 of EP ’243 means that “there are an infinite number of different potential compositions of the buffer that would fall within the characteristics of the buffer as described in EP ’243.” (Tr. 1614:9-24 (Thomson), May 16, 2014; *see also* Tr. 651:21-23 (Miller), May 9, 2014.)

“[I]t is understood that small changes in those compounds or even the changes in the concentration of the compounds, can result in significant changes in any antimicrobial activity that the compound might have.” (Tr. 652:3-9 (Miller), May 9, 2014; *see also* Tr. 652:10-12 (Miller), May 9, 2014 (testifying that “small changes can result in significant changes in the antimicrobial activity” is “true”).) Experts for both parties agree that in order “[t]o determine which of those infinite number of solutions could selectively kill gram negative bacteria and inhibit gram positive

²³ The Federal Circuit uses criteria that are referred to in the case law as the *Wands* factors in determining whether a prior art reference requires undue experimentation for anticipation. *Id.* at 1054-55. These include: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *Id.*

²⁴ UTC argues that the standard applied by Sandoz is inapposite. Specifically, UTC argues that Sandoz never analyzed whether EP ’243 enables the claims of *the ’007 patent*. Instead, UTC argues, Sandoz examined whether EP ’243 teaches one of ordinary skill in the art to carry out the claims of the EP ’243 application without undue experimentation. (*See, e.g.*, Sandoz Trial Br. [D.I. 242] at 30.)

bacteria,” a person of ordinary skill in the art “would have to perform [] antimicrobial effectiveness test[s].” (Tr. 653:11-16 (Miller), May 9, 2014.); (Tr. 1618:9-22 (Thomson), May 16, 2014) (stating that a person of ordinary skill in the art “would have to do some testing to determine whether or not gram negative bacteria or gram positive bacteria survive.”) Furthermore Dr. Miller testified that “[D]etermin[ing] the compatibility of antimicrobial agents with other components in the [EP ’243 Example 1] solution” would require “a lot of testing” (Tr. 653:17-654:1 (Miller), May 9, 2014.)

The parties’ experts agree that “[T]here’s no [such] testing in EP ’243 of whether or not bacteria survive,” and “EP ’243 does not include the results of any testing on whether or not the gram negative or gram positive bacteria survive in the solution described in example 1.” (Tr. 1618:25-1619:7 (Thomson), May 16, 2014; *see also generally* PTX-316.);(Tr. 654:13-655:6 (Miller), May 9, 2014.)(“[T]here [is] nowhere in the prior art that discloses selectively killing gram negative bacteria,” which means that “a person of ordinary skill in the art reading EP ’243 would not be able to make and use or practice the ’007 invention” because of “how unpredictable formulations can be in terms of antimicrobial effectiveness.”). Therefore, a person of ordinary skill in the art could not know whether this “infinite number of solutions selectively kill gram negative bacteria and inhibit the growth of gram positive bacteria.” (Tr. 651:24-652:2 (Miller), May 9, 2014.)

Consequently, in light of the infinite number of possibilities and the Court’s consideration of “quantity of experimentation under *Wands*, the Court finds that “a person of ordinary skill in the art reading EP ’243 would not be able to practice the ’007 patent claims without undue experimentation.” (Tr. 651:5-14 (Miller), May 9, 2014.) Sandoz has failed to prove by clear and convincing evidence that EP ’243 enables a skilled artisan to practice the claims of ’007.

Conclusion

For the reasons explained above, the Court concludes EP ’243 could not have anticipated the ’007 patent because – at the time of the ’007 invention – it would not have enabled a person to

practice the claims of the '007 invention without undue experimentation. Furthermore, it is undisputed that EP '243 says nothing about bacteria, bloodstream infections, sepsis, antimicrobial effectiveness testing or data, or any potential antimicrobial properties. Thus, EP '243 could not “describe ... [the] claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention” as required to qualify as an anticipatory reference. *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000). As explained below, the Court concludes that “EP '243 does not enable any of the '007 patent claims, whereas “EP '243 provides no direction that would get a person of ordinary skill to the '007 patent” and “provides no working examples.” (Tr. 654:13-655:6 (Miller), May 9, 2014.)

Obviousness

As previously noted, obviousness is a question of law that is predicated on several factual findings. See *Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The trier of fact is directed to assess four considerations specifically: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. See *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

Differences Between the '007 Patent Claims and the Prior Art, EP'243

The '007 Asserted Claims are not rendered obvious by EP '243 alone or in combination with the 2006 Remodulin package insert and/or the 1999 Flolan package insert. (Tr. 678:18-679:5 (Miller), May 9, 2014.) As set forth above, the Court finds that EP '243 does not disclose or suggest all the elements of independent claims 1 or 11 or their dependent claims. The Court further finds that neither the 2006 Remodulin nor the 1999 Flolan package inserts work to cure those deficiencies by supplying any of the elements missing from the disclosure of EP '243. (Tr. 646:15-647:2, 673:12-19 (Miller), May 9, 2014; Tr. 1582:5-8, 1582:22-1583:1, 1583:5-1584:9, 1587:12-23,

1638:22-1640:23, 1641:6-14, 1641:19-23 (Thomson), May 16, 2014; PTX-316; DTX-147; DTX-148.)

(i) *Independent Claim 1*

Independent claim 1 of the '007 patent claims “[a] method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation.” (PTX-003 at 7:58-60.) As set forth in detail above, this Court finds that EP '243 does not teach or disclose any of the antimicrobial properties required by claim 1 of the '007 patent. This Court further finds that neither the Remodulin Insert nor the Flolan Insert cures that deficiency. Nothing in the Remodulin package insert specifically addresses the method of selectively killing gram negative and inhibiting the growth of gram positive bacteria. (Tr. 1639:24-1640:5 (Thomson), May 16, 2014.) As such, experts for both sides recognize that, “nothing in the Remodulin package insert makes the method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria obvious.” (Tr. 1640:6-10 (Thomson), May 16, 2014; *see also* Tr. 656:16-657:7, 678:16-22 (Miller), May 9, 2014.)

Similarly, “the Flolan package insert does not teach any selectively killing of gram negative bacteria and inhibiting the growth of gram positive bacteria.” (Tr. 1641:6-9 (Thomson), May 16, 2014.) The 1999 Flolan package insert does not include any mention of treprostinil, treprostinil solutions prepared with high pH glycine diluents, the potential antimicrobial (bactericidal or inhibitory) properties of any particular diluent (including a high pH glycine buffer), antimicrobial effectiveness testing, or any other such disclosures or data. (Tr. 1641:6-14; 1641:19-23 (Thomson), May 16, 2014; DTX-147.) Accordingly, experts for both sides recognize that, “nothing in the Flolan package insert would make selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria obvious.” (Tr. 1641:10-14 (Thomson), May 16, 2014; *see also* Tr. 676:14-677:23 (Miller), May 9, 2014.)

On these facts, the Court concludes that “the combination of EP '243, with the Remodulin package insert, and/or the 1999 Flolan package insert” do not “disclose or suggest all of the elements of any of the '007 patent claims.” (Tr. 679:1-5 (Miller), May 9, 2014.)

Level of Ordinary Skill: A Person of Ordinary Skill Would Not Have Combined the High pH Flolan Diluent with Remodulin Because the Stability Profiles and Diluent Labels Taught Away From the Combination

As previously noted, in order to prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), cert. denied, 133 S. Ct. 933, 184 L. Ed. 2d 725 (U.S. 2013) (citing *Procter & Gamble*, 566 F.3d at 994). For the reasons that follow, this Court finds that a skilled artisan would not have combined SDF with Remodulin in light of the fact that stability profiles and the product labels themselves taught away from such a combination.

Prior to the invention of the '007 patent, "the primary concerns of a person of ordinary skill preparing a formulation of treprostinil for the tests that were disclosed in EP '243" would be "to ensure that the composition was stable, safe, and effective." (Tr. 671:8-13 (Miller), May 9, 2014; see also Tr. 1512:24-1515:1 (Thomson), May 15, 2014.)

Experts for both parties emphasized the significance of the choice of diluent when administering drugs to a patient intravenously. Plaintiff's expert, Dr. Miller specifically highlighted stability concerns. Dr. Miller testified that at the time of the '007 patent, a skilled artisan would have understood that Remodulin is diluted with either sterile water or a saline because, as pH neutral diluents, they each provide for a stable pharmaceutical composition. See (Tr. 674:17-23, 675:1-7 (Miller), May 9, 2014; DTX-148 at Sandoz-Trep 0004343.) Dr. Miller further testified that Flolan, on the other hand, cannot be administered in sterile water or saline "because it's unstable" in such an environment. (Tr. 677:14-16 (Miller), May 9, 2014; DTX-147 at Sandoz-Trep 0004305.)

For his part, Defendant's expert, Dr. Thomson, highlighted other safety concerns. Dr. Thompson testified that at the time of the '007 patent application, it was known that "high pH formulations cause" significant complications for patients, such as "the lysis of blood cells during administration." (Tr. 1642:7-11 (Thomson), May 16, 2014.) Dr. Thomson further testified that "[i]t would have been "very unusual" to select a high pH buffer for a parenteral solution like Remodulin as a result, (Tr. 1513:7-11 (Thomson), May 15, 2014), with artisans preference "to make preparations" for parenteral administration "closer to neutral pH" of 7 than a high pH of 10.5. (Tr. 1513:11-12 (Thomson), May 15, 2014.)

"[P]rior to th[e] priority date of the '007 patent, there was no publication that identified the differences in the diluents of Remodulin and Flolan, as being either the cause or the solution to the differences in the infection rate between I.V. Remodulin patients and I.V. Flolan patients." (Tr.

1653:12-18 (Thomson), May 16, 2014.) Moreover, Sandoz has presented no evidence that prior to the '007 patent, treprostinil had ever been tested for stability, solubility, and compatibility in a high pH diluent. These facts, taken in light of the stability and safety concerns highlighted by both Dr. Miller and Dr. Thomson, lead this Court to find that, prior to the invention of '007, a person of ordinary skill in the art would not have had any reason or incentive to risk “administer[ing] treprostinil in a diluent other than saline or water” whereas those diluents “provide[d] for a stable pharmaceutical composition for administration.” (Tr. 675:8-12 (Miller), May 9, 2014.)

The Court further finds that its reasoning is not swayed by further consideration of the Remodulin and Flolan Inserts. The 2006 Remodulin package insert does not include any mention of treprostinil solutions prepared with high pH glycine diluents. (Tr. 671:14-17 (Miller), May 9, 2014; DTX-148.) The “FDA approved labeling” for the Sterile Diluent for Flolan as that labeling existed prior to the '007 patent stated the vial “contains drug diluent for use *only* with Flolan, epoprostenol sodium for injection.” (Tr. 1646:2-22 (Thomson), May 16, 2014 (emphasis added).) Based on the disclosures of these package inserts, “the skilled artisan would not have had any reason to reformulate a stable treprostinil product with a higher [than neutral] pH diluent.” (Tr. 671:24-672:10 (Miller), May 9, 2014.)

Accordingly, this Court concludes that “at the time of the '007 patent invention, a person of ordinary skill reading EP '243 ... the 2006 Remodulin package insert, the 1999 Flolan package insert” would have had “no motivation and no reason” to “make or use the invention of the '007 patent.” (Tr. 677:24-678:15 (Miller), May 9, 2014.) . To find otherwise would impermissibly rely on hindsight.

(ii) Dependent Claims 2-5, 7-10, & 21

Claims 2-5, 7-10, and 21 of the '007 patent are each dependent on claim 1 and include all the limitations of claim 1. As set forth above, the prior art did not disclose, teach, or render obvious claim 1 of the '007 patent. For the same reasons, the prior art did not disclose, teach, or render obvious the inventions of claims 2-5, 7-10, and 21.

(iii) Independent Claim 11

Claim 11 requires “[a] method of reducing the occurrence of blood stream infections in a mammal being treated with an active agent.” (PTX-003 at 8:20-21.)

As previously noted, before the '007 patent, "there was no publication that identified the differences in the diluents of Remodulin and Flolan, as being either the cause or solution to the differences in the infection rate between I.V. Remodulin patients and I.V. Flolan patients." (Tr. 1653:12-18 (Thomson), May 16, 2014.) Before the priority date of the '007 patent, the prior art does not include "any authors discussing the pH of the diluents" for Remodulin and Flolan "in connection with the bloodstream infection rates." (Tr. 1651:8-1652:11 (Thomson), May 16, 2014.) There is no "evidence before the '007 patent priority date that the subject matter of the asserted claims resulted in a reduction of blood stream infections." (Tr. 1582:22-1583:1 (Thomson), May 16, 2014.) ²⁵As set forth above, the prior art did not disclose, teach, or suggest "[a] method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria." For the same reasons, the prior art also did not disclose, teach, or suggest "reduc[ing] the gram negative bacteria and inhibit[ing] the growth of gram positive bacteria" as required by claim 11.

(ix) *Dependent Claims 12-17, 19-20*

Claims 12-17, 19-20 are each dependent on claim 11 and include all the limitations of claim 11. As set forth above, the prior art did not disclose, teach, or render obvious claim 11 of the '007 patent. For the same reasons, the prior art did not disclose, teach, or render obvious the inventions of claims 12-17, 19-20.

(xv) *Claim 23*

Claim 23, which depends from claim 22, requires a "pharmaceutical composition" of treprostinil combined with a high pH glycine buffer. (PTX-003 at 8:52-57.) EP '243 (alone or in combination with other references) does not disclose or render obvious the "pharmaceutical composition" required by claim 23. (Tr. 666:12-20 (Miller), May 9, 2014.) Although EP '243 claims certain medicaments or pharmaceutical compositions, it never identifies the test compound

²⁵ As Sandoz expert Dr. Thomson admitted, "EP '243 does not teach any method of reducing the occurrence of bloodstream infections" as recited in claim 11. (Tr. 1583:13-16, 1639:1-4 (Thomson), May 16, 2014.) Dr. Thompson also testified that the "Remodulin package insert does not teach reducing the occurrence of bloodstream infections by using a high pH diluent with low buffer capacity." (Tr. 1640:14-18 (Thomson), May 16, 2014.) "[N]othing in the Remodulin package insert would make the method of reducing the occurrence of bloodstream infections in claim 11 of the '007 patent obvious." (Tr. 1640:19-23 (Thomson), May 16, 2014.) Dr. Thompson similarly conceded "[N]othing in the Flolan package insert addresses the method of reducing the occurrence of bloodstream infections." (Tr. 1641:15-18 (Thomson), May 16, 2014.) "[N]othing in the Flolan package insert would make the method of reducing the occurrence of bloodstream infections in claim 11 and its dependent claims obvious." (Tr. 1641:19-23 (Thomson), May 16, 2014.)

of Example 1 as a medicament or pharmaceutical composition; to the contrary, it is identified only as a “test compound.” (PTX-316 at Sandoz-Trep 0006971; Tr. 1647:17-1648:18 (Thomson), May 16, 2014.)

A person of ordinary skill in the art would understand that “test compounds” used in animal studies are not necessarily pharmaceutical compositions. (Tr. 670:7-9 (Miller), May 9, 2014.) As set forth above, it would not have been obvious to combine treprostinil and a high pH buffer because of stability, solubility, and compatibility concerns. Accordingly, the high pH “pharmaceutical composition” of claim 23 would not have been obvious to a person of ordinary skill in the art. (Tr. 672:11-21 (Miller), May 9, 2014.)

Secondary Considerations of Non-Obviousness

In evaluating obviousness, courts must consider objective evidence of nonobviousness in the form of secondary considerations, as that “may often be the most probative and cogent evidence in the record” related to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Here, UTC points to unexpected results, satisfaction of a long-felt but unsolved need, failure of others, initial skepticism followed by industry acceptance, and commercial success as objective evidence of nonobviousness.

Long-felt but Unsolved Need, Failure of Others, and Unexpected Results

UTC contends that prior to the ’007 invention, there was a long-felt but unsolved need among physicians who prescribe (and patients who receive) intravenous Remodulin to ensure the safety of its administration. (Tr. 1667:3-12 (White), May 16, 2014.) UTC describes the demand to address the increased BSI problem identified by Dr. Barst as “intense and significant”. See UTC Brief at p. 36. As explained by Plaintiff’s expert, Dr. White, the BSI problem was the source of “a large expenditure of healthcare resources, [and] ... a lot of morbidity and in fact death.” (See Findings of Fact 124-126 and 133, *supra*; Tr. 1670:14-1671:11 (White), May 16, 2014.)

Dr. White testified that following Dr. Barst’s discovery, many experts in the field focused intently on the problem. Indeed, UTC presented evidence that, prior to the date of the invention, doctors at the CDC worked with other experts in the field to identify theories for the increased incidence of BSIs in intravenous Remodulin patients. (Tr. 1675:23-1677:10 (White), May 16, 2014.) The CDC conducted a survey by which they identified three theories for the increased rate of

BSIs in the CDC Survey; yet the survey did not “mention[] the Sterile Diluent for Flolan as a potential solution of the problem.” One of the CDC’s three theories was “a rather fantastic idea, which is that Remodulin somehow accept suppressed the body’s immune system, somehow makes people more susceptible to a bacterial infection. So it reaches for ... pretty fantastic hypotheses, and yet doesn’t mention the use of SDF.” (Tr. 1676:19-1677:6 (White), May 16, 2014.)

The Court accepts the CDC Survey as evidence demonstrating both a long-felt yet unsolved need and a failure of others to identify SDF as a solution to the BSI problem. Given the significant attention to this issue among experts in the community, and the resources dedicated to researching the BSI problem, the Court accepts Dr. White’s assertion that “if somebody expected SDF to work in this way, [the CDC] would have mentioned it.” (Tr. 1677:7-10 (White), May 16, 2014; *see also* Tr. 1673:1-18 (White), May 16, 2014 (“[The CDC] conclude basically that we need more information.”); PTX-995 at UTC-Sand-Rem 01169630.)

In light of expert testimony from Dr. White, Dr. Zaccardelli, Dr. Thompson, and Dr. Miller, the Court further accepts the CDC survey as evidence which sufficiently demonstrates that UTC’s results with the ‘007 patent were unexpected. Dr. White testified that before the invention, “the people who [were] very familiar with Flolan[] never offered the idea of Sterile Diluent for Flolan as a potential solution” to the BSI problem with intravenous Remodulin. (Tr. 1674:20-24, 1676:19-24, 1677:11-17 (White), May 16, 2014.) Moreover, the CDC survey objectively supports that testimony. Dr. White explained the perspective of a treating physician, acting prior to the ‘007 patent invention, as follow:

“[N]ot like today, in 2006 and in 2007 most physicians who are going to write a prescription for Remodulin are Flolan users. They know Flolan well. Flolan is on their shelf, it’s the thing that they are most comfortable reaching for and Remodulin is new. And they know Sterile Diluent for Flolan.” (Tr. 1676:4-9 (White), May 16, 2014.) But these prescribers thought of SDF as a “high pH buffer [that is] necessary to dissolve the powdered Flolan, and ... necessary to keep Flolan stable, for administration to a patient through a pump. ... What they didn’t know, and what the inventors of the ‘007 patent determined, was that Flolan Sterile Diluent also kills gram negative bacteria. They didn’t know that Sterile Diluent for Flolan was actually protecting their [Flolan] patients, from these gram negative bacteria.” (Tr. 1676:9-18 (White), May 16, 2014.)

UTC’s expert, Dr. Miller, similarly testified that “selectively killing of gram negative bacteria, inhibition of gram positive bacteria ... was actually very surprising to me because I’ve been

conducting antimicrobial effectiveness tests with these same microorganisms for most of my career, and this type of a profile is not something I've seen in the past.” (Tr. 693:20-694:3 (Miller), May 9, 2014.)

Given that Sandoz's own expert, Dr. Thompson, testified that “prior to th[e] priority date of the '007 patent, there was no publication that identified the differences in the diluents of Remodulin and Flolan, as being either the cause or the solution to the differences in the infection rate between I.V. Remodulin patients and I.V. Flolan patients,” (Tr. 1653:12-18 (Thomson), May 16, 2014.) the Court finds that the testimony of Dr. Miller and Dr. White is persuasive in light of the objective CDC survey corroborating same. Accordingly, the secondary considerations of long-felt but unsolved need, failure of others, and unexpected results each weigh in favor of a finding of nonobviousness.

Commercial Success

The plaintiffs assert that the commercial success of Lyrica[®] is evidence of the non-obviousness of the patents-in-suit. Importantly, commercial success is “only significant if there is a nexus between the claimed invention” and the secondary consideration at issue. *See, e.g., Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). Commercial success is an indication of nonobviousness “because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art.” *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005).

As set forth above, the administration of Remodulin in SDF practices the Asserted Claims of the '007 patent. In view of record before it, the court concludes that the plaintiffs have demonstrated (1) that Remodulin is a commercial success and (2) that Remodulin's success is attributable in part to the '007 patent.

“Commercial success is one of the indicators” Sandoz generally looks for in determining whether it will offer a generic version of a drug. (Tr. 2173:19-24 (Nandi), May, 27, 2014.) It is undisputed that Remodulin would be highly profitable for Sandoz. Indeed, Sandoz's witnesses testified: that “[t]he most important consideration in assessing whether a project is high value [is] the financial success of the project.” (Tr. 2214:6-13 (Petek), May 27, 2014.), and that Sandoz considered its ANDA for treprostinil to be its “single most high-value, first-to-file [ANDA] for the US in 2011.” Sandoz agreed that if Sandoz maintains its “exclusive first to file” status, it will have

“180 days of exclusivity after [the] launch of [its] generic product,” which would result in “significant additional revenues.” (Tr. 2210:12-2211:13 (Petek), May 27, 2014; PTX-374 at Sandoz-Trep 0024641.)

Plaintiff’s also submitted substantial evidence that “there is ... a nexus between the ’007 patent and the commercial success of Remodulin.” (Tr. 1915:14-21, 1927:6-1930:16 (Gering), May 19, 2014; PTX-971; DTX-129.) Accredo, a specialty pharmacy distributor, which represents approximately 80 percent of the market for Remodulin sales in the US, tracks the total number of IV patients on a monthly basis going back to 2009. (Tr. 1926:20-1927: 3, 1928:4-1929:4 (Gering), May 19, 2014; PTX-971; PTX-973; DTX-129.) Data from Accredo reveals that the rate of SDF use rose from 15.5 percent in September 2009, to 35.8 percent in September 2010, to 41.2 percent in September 2011, and to 46.0 percent in September 2012. (PTX-973 at UTC-Sand-Rem 01169472; PTX-538 at UTC-Sand-Rem 00067113; PTX-912 at UTC-Sand-Rem 01162346; PTX-534 at UTC-Sand-Rem 00067065; *see also* Tr. 339:2-340:16 (White), May 7, 2014; Tr. 1690:3-21 (White), May 16, 2014.) The Accredo data also shows that there has been an increase in SDF use coupled with a dramatic decrease in sterile water and a decrease in saline, reflecting that there is a switch from sterile water and from saline towards SDF. (Tr. 1928:4-19 (Gering), May 19, 2014; PTX-971; PTX-973; DTX-129.)

Furthermore, Sandoz’s expert, Dr. Vander Veen, admitted that Remodulin has been a commercial success. (Tr. 1321:12-15 (Vander Veen), May 14, 2014.) Dr. Vander Veen further acknowledged that patients switching to the patented method and composition is an indication that there is a nexus between the patented method and its commercial success (Tr. 1319:9-13, 1320:2-4 (Vander Veen), May 14, 2014.) Based on a chart out of his own report, Dr. Vander Veen admitted “[f]or the time period September 2009 through September 2013 it appears that the Flolan diluent has replaced the sterile water.” (Tr. 1336:16-18 (Vander Veen), May 14, 2014.) In light of these figures and the evidence in the record, the Court concludes that UTC has established evidence sufficient to demonstrate commercial success attributable to the ’007 patent.

Initial Skepticism Followed by Industry Acceptance

A court assessing secondary considerations in an obviousness analysis may consider evidence of substantial industry recognition where it is presented to rebut the defendants’ *prima facie* case of obviousness. *See Ortho McNeil Pharm., Inc. v. Mylan*, 520 F.3d 1358, 1365 (Fed. Cir.

2008). Here, the plaintiffs presented persuasive evidence of industry recognition at trial. Specifically, UTC presented testimony through Dr. White that there was initial skepticism about the '007 invention among practitioners who “didn’t believe that it was going to work” which was eroded after the *in vitro* data corroborating the results of the '007 patent were released to the public, and thus made readily available to practitioners, in 2010 with the publication of the Zaccardelli article. Dr. White explained that the invention described and claimed in the '007 patent now enjoys broad acceptance in the industry, as evidenced by a “near tripling of the use of SDF as a fraction of all the [intravenous Remodulin] prescriptions written.” (Tr. 1690:3-1691:7 (White), May 16, 2014.)

The Court finds that Dr. White’s testimony is not only corroborated by the Accredo sales data; it is also supported by published literature which reveals that many practitioners who treat pulmonary hypertension now, in fact, consider the use of SDF with IV Remodulin to be a best practice. (Tr. 1690:3-21; 1695:3-1696:10 (White), May 16, 2014; PTX-534 at UTC-Sand-Rem 00067072.) The Rich study “concludes that [the use of SDF] ought to be a best practice.” (Tr. 1695:3-10 (White), May 16, 2014.) Separately, the authors of the Kitterman study, who are “luminaries in the field” not among the authors of the Rich article, include use of SDF as one of the “recommended best practice guidelines” for administering Remodulin. (Tr. 1695:11-25 (White), May 16, 2014; *see also* PTX-912 at UTC-Sand-Rem 01162352; PTX-534 at UTC-Sand-Rem 00067072-73.)

The Asserted Claims of the ‘007 Patent Are Not Obvious In Light of Prior Art

Based on the aforementioned facts and findings, the Court concludes that the prior art taught away from combining treprostinil and a high pH buffer because of stability, solubility, and compatibility concerns. Such an administration of treprostinil would not have been obvious to a person of ordinary skill in the art prior to the invention of the '007 patent. In light of substantial evidence of secondary considerations weighing in favor of nonobviousness, the Court hereby concludes that the '007 was not obvious to a skilled artisan prior to the date of invention.

4. Indefiniteness

As the Supreme Court recently noted, “in assessing definiteness, claims are to be read in light of the patent’s specification and prosecution history” and “evaluated from the perspective of someone skilled in the relevant art” “at the time the patent was filed.” *Nautilus, Inc. v. Biosig*

Instruments, Inc., 134 S. Ct. 2120, 2128 (2014).

Sandoz's indefiniteness analysis, as presented by Dr. Thomson, relies exclusively on the language of the claims, which Dr. Thomson contends are impossible to understand. (Tr. 1532:8–1533:3, 1536:9–1537:19 (Thomson), May 15, 2014.) In so doing, Sandoz fails to heed the Supreme Court's requirements that claims must be assessed from the perspective of a person of ordinary skill "in light of the patent's specification and prosecution history." *Nautilus*, 134 S. Ct. at 2128.

a) Claim 12

Claim 12 depends from claim 11 of the '007 patent. Claim 11 recites:

A method of reducing the occurrence of blood stream infections in a **mammal** being treated with an active agent comprising administering to the **mammal** the active agent with a buffer comprising glycine and having a pH of greater than 10, wherein the active agent is selected from the group consisting of treprostinil and treprostinil sodium, and wherein the administration reduces the gram negative bacteria and inhibits the growth of gram positive bacteria.

(Tr. 603:2-4 (Miller), May 8, 2014; PTX-003 at 8:20-27 (emphasis added).) Claim 12 recites:

The method of claim 11, wherein **the human subject** has pulmonary arterial hypertension." (PTX-003 at 8:28-29 (emphasis added).)

"[T]he term mammal and the term human subject ... are not technical words" and are "readily understood by the skilled artisan. A person of ordinary skill would not confuse the term human subject with a cat or a rabbit or a dog." (Tr. 695:17-22 (Miller), May 9, 2014.)

The '007 patent specification makes clear that "the human subject" refers to a person or human being. "[W]hen one reads the '007 patent specification, it's very clear that the patent is talking about a human subject. Because ... we're talking about patients in hospital environments, medical devices and medicines, such as Remodulin and Flolan that have been approved for use in human patients." (Tr. 696:2-7 (Miller), May 9, 2014; *see also* PTX-003 at 3:67-4:5 ("Gram negative bacteria are a common source of infection in hospital environments ..."), 5:9-20 (discussing administration of treprostinil via "a SIMS Deltac, Inc. CADD Legacy™ 1 (Model 6400) Pump delivery device"), 5:56-62 (discussing experiments in Remodulin and Flolan).)

A person of ordinary skill in the art would readily understand that '007 patent claim 12 limits claim 11 by narrowing the class of subjects included in the claim from "mammals" to the

more restrictive, narrower class of “humans.” “[I]t’s understood that human[s] are a subset of mammals, and so when we see the term human subject in claim 12, that’s just narrowing that class of mammals that we find in the previous claim in claim 11.” (Tr. 695:23-696:1 (Miller), May 9, 2014; PTX-003 at 8:20-29.)

To the extent that Dr. Thomson’s indefiniteness analysis pertaining to claim 12 relies exclusively on the language of the ’007 patent claims, and does not consider the specification or prosecution file history, (*See* Tr. 1532:8-1533:3 (Thomson), May 15, 2014.) the Court concludes that it is improper.

b) Claim 21

Claim 21 depends from claim 1 of the ’007 patent. Claim 1 recites:

A method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium, the method comprising **supplying the active agent** with a buffer comprising glycine and having a pH of greater than 10 with low buffer capacity.

(PTX-003 at 7:58-65 (emphasis added).) Claim 21 recites:

The method of claim 1 wherein **the administering** is injecting the pharmaceutical preparation into a mammal in need thereof.

(PTX-003 at 8:49-5 (emphasis added).)

A person of ordinary skill in the art reading claim 21 would understand that “the administering” as recited in claim 21 is a manner of “supplying the active agent” as recited in claim 1. (Tr. 694:17-21 (Miller), May 9, 2014; PTX-003 at 7:58-65, 8:49-51.) A person of ordinary skill in the art would understand that “the administering” is referring to “injecting the pharmaceutical preparation into a mammal in need thereof” as further recited in claim 21. (Tr. 694:22-24 (Miller), May 9, 2014; PTX-003 at 8:49-51.) “[T]he term, administer, has a very readily discernible meaning to a person of ordinary skill” because “[t]he term is used throughout the patent specification, and it’s also used in claim 11 ... and Sandoz is not contending that claim 11 is indefinite.” (Tr. 694:25-695:5 (Miller), May 9, 2014; *see* PTX-003 at 1:26-28 (“The use of buffers to maintain a pH and solubilize or dilute active pharmaceutical agents (‘APIs’) before *administration* (e.g., by injection)

is routine.” (emphasis added)), 1:39-41 (“[G]ram negative bacteria are associated with water contamination which can occur with chronic indwelling catheters such as used with intravenous *administration*.” (emphasis added)), 2:11-20 (“In another embodiment of the invention, a method of reducing the occurrence of blood stream infections in a mammal being treated with an active agent is provided, the method comprising *administering* to the mammal the active agent with a buffer having a pH of greater than about 10 or less than about 4.5 and a low buffer capacity, wherein the active agent is not epoprostenol sodium, and wherein the *administration* reduces the gram negative bacteria and inhibits the growth of gram positive bacteria. In some cases, the human subject may suffer from pulmonary arterial hypertension.” (emphasis added)), 8:20-27 (claim 11 recites “[a] method ... comprising *administering* to the mammal the active agent with a buffer ...” (emphasis added)).) Claim 21 is not indefinite because “in reviewing this Court’s *Markman* order, there’s a related term, administration, that appears in a claim limitation that should be given its plain and ordinary meaning.” (Tr. 695:6-9 (Miller), May 9, 2014; June 25, 2013 *Markman* Order [D.I. 95] at 25 (ordering that “wherein the *administration* reduces the gram negative bacteria and inhibits the growth of gram positive bacteria” requires no construction) (emphasis added).)

To the extent that Dr. Thomson’s indefiniteness analysis pertaining to claim 21 relies exclusively on the language of the ’007 patent claims, and does not consider the specification or prosecution file history, the Court concludes that it is improper. (See Tr. 1536:9-1537:19 (Thomson), May 15, 2014.)

Conclusion

Based on the foregoing facts and findings, the Court concludes that Defendant have failed to prove by clear and convincing evidence that the ’007 patent claims are indefinite. Therefore, Defendant had failed to prove by clear and convincing evidence that the ’007 is invalid.

B. Validity of the ’117 Patent

1. Scope and Content of the Prior Art

Dr. Paul Aristoff is the sole inventor of the only prior art reference that Sandoz contends invalidates the ’117 patent – U.S. Patent No. 4,668,814 (“the ’814 patent”). (Tr. 1726:24-1727:10, 1731:1-2 (Aristoff), May 16, 2014; DTX-55 at Sandoz-Trep0079205.) The ’814 patent discloses a synthesis to make benzindene prostacyclin analogs including treprostinil in Example 3. (Tr. 1436:5-

12 (Buchwald), May 15, 2014; DTX-55 at 29:12-33:4.) The synthesis allowed Dr. Aristoff to make gram scale quantities of material. (Tr. 1731:3-8 (Aristoff), May 16, 2014; DTX-55.)

The '814 patent discloses a synthesis for treprostinil that produces a 1:1 mixture of diastereomers in the last seven steps of the synthesis. (Tr. 1721:8-22, 1736:21-1738:8, 1740:20-1741:3 (Aristoff), May 16, 2014.)

The only purification procedure for the final step of making treprostinil described in the '814 patent is limited to taking "[t]he resulting pink to red solid was chromatographed on 400g of CC-4 acid washed silica gel eluting with 2L of 50% ethyl acetate in hexane ... to give 5.10g of solid which was crystallized from hot tetrahydrofuran and hexane to give 1.20g of" the molecular name that corresponds to treprostinil. (Tr. 1436:13-1437:1 (Buchwald), May 15, 2014; DTX-055 at Sandoz-Trep0079221.) The resulting 1.20g of treprostinil described in the '814 patent was not pure. (Tr. 1437:7-9 (Buchwald), May 15, 2014; DTX-055 at Sandoz- Trep0079221.)

The '814 patent disclosed a two degree melting point range of 122 to 124 degrees for the 1.20g sample of treprostinil and a person of ordinary skill in the art could not distinguish a 95% pure sample from a 98% pure sample with that range. (Tr. 1437:2-6, 1438:13-18 (Buchwald), May 15, 2014; DTX-055 at Sandoz- Trep0079221.)

From commercially available starting materials, the overall yield of treprostinil from the synthesis disclosed in the '814 patent was 0.3%. (Tr. 1741:19-24 (Aristoff), May 16, 2014.) Two-thirds of the product material for treprostinil is lost in the last step of the '814 patent synthesis to remove the unwanted diastereomer and there were low yields in the other steps as well. (Tr. 1738:9-1739:2 (Aristoff), May 16, 2014.)

2. *Anticipation*

The legal principles articulated above with respect to the '007 patent generally remain true for the '117 patent with some exceptions. Those exceptions stem from the fact that the '117 patent claims are product-by-process claims. This difference in claim structure alters the analysis for anticipation and obviousness, which are the only grounds of invalidity Sandoz asserts for the '117 patent. If the claim is a product-by-process claim, the focus of the anticipation analysis is the product produced by the claimed process. *Amgen*, 580 F.3d at 1369–70. The prior art does not need to teach the process limitations so long as the prior art product is the same as the claimed product. *Id.* (citations omitted).

Notably, this anticipation analysis differs significantly from the *infringement* analysis employed above, because “[i]n determining infringement of a product-by-process claim . . . , the focus is on the process of making the product as much as it is on the product itself.” *Id.* (citing *Abbott Labs. v.*, 566 F.3d at 1293). While anticipation does not focus on the process limitations, the claimed product may have structural and functional features, including unclaimed features, imparted by the process that differentiate the claimed product from the prior art. *Id.* at 1370; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006) (“If those product-by-process claims produced a different product than that disclosed by the [prior art], there would be an argument that the [prior art] did not anticipate.”); *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 9, Aug. 2012) (structure implied by process steps can differentiate a claim over the prior art). In other words, the process can impart unclaimed characteristics to the product that differentiate it from the prior art. Structural differences alone may distinguish the prior art. *Greenliant Sys. v. Xicor LLC*, 692 F.3d 1261, 1269–71 (Fed. Cir. 2012).

Sandoz contends that U.S. Patent No. 4,668,814 (“the ‘814 patent”), anticipates the ‘117 Asserted Claims because the ‘814 patent discloses treprostinil and the pharmacologically acceptable salt form of treprostinil. (Tr. 1431:13-17 (Buchwald) May 15, 2014.). However, UTC maintains that the stereoselectively produced isomeric compound of the ‘117 patent is not the same as treprostinil found in the prior art. Specifically, UTC argues that significant differences in the claimed product—revealed by the totality of the evidence presented through expert testimony—mean that the claims of the ‘117 patent are not anticipated by the ‘814 patent. The Court agrees with UTC.

For the reasons set forth below, the Court concludes that Sandoz has failed to prove by clear and convincing evidence that ‘117 patent claims are anticipated by the ‘814 patent.

a) Independent Claim 1

The ‘814 patent does not disclose the intramolecular cyclization step, the starting enyne compound, or the cyclized intermediate compound required by claims 1-4 of the ‘117 patent

Several claim limitations present in the ‘117 patent are not disclosed in the ‘814 patent. The intramolecular cyclization step required by claims 1-4 of the ‘117 patent is not disclosed in the ‘814 patent. (Tr. 1732:10-11 (Aristoff), May 16, 2014; DTX-55.) The ‘814 patent does not disclose the

starting enyne compound required by claims 1-4 of the '117 patent. (Tr. 1732:1-4 (Aristoff), May 16, 2014; DTX-55.) The '814 patent does not disclose the cyclized intermediate compound required by claims 1-4 of the '117 patent. (Tr. 1732:5-9 (Aristoff), May 16, 2014; DTX-55.) Dr. Buchwald agrees that the '814 patent does not disclose the starting enyne, intramolecular cyclization step, or the cyclized intermediates present in the claims of the '117 patent. (Tr. 1435:25-1436:4 (Buchwald), May 15, 2014.)

The '814 patent does not disclose a “stereoselectively produced isomeric compound” of treprostinil.

Dr. Buchwald relied on a reference, “Stereochemistry of Organic Compounds” that defines “stereoselective” as “used to describe the stereochemical outcome of a reaction when it was possible for more than one stereoisomer to be formed, but one is formed in excess, although its use should desirably be restricted to situations where the proportion of the major stereoisomer is substantially greater than that of the minor one(s). (Seebach et al., 1986).” (Tr. 1419:15-1420:24 (Buchwald), May 15, 2014; PTX-480 at Sandoz-Trep0084014.) Dr. Buchwald agreed with this definition of stereoselective and noted the author of the definition was “an extraordinary expert in terms of nomenclature, rather than an ordinary expert in terms of nomenclature...” (Tr. 1420:25-1421:7 (Buchwald), May 15, 2014; PTX-480 at 837.)

A person of ordinary skill in the art would realize as soon as you look at the '814 patent that you prepare a one-to-one (or 50/50) mixture at the final step which is not stereoselective. (Tr. 1731:21-25 (Aristoff) May 16, 2014; DTX-55 ('814 patent).) Dr. Buchwald concedes that some skilled artisans would not think that a 50/50 mixture of diastereomers at the end of a reaction sequence is stereoselective. (Tr. 1421:12-14, 1422:3-12 (Buchwald), May 15, 2014.)

As explained in detail below, for his part, Dr. Aristoff had “no doubt” that none of the prior art references including the '814 patent disclosed a “stereoselectively produced” treprostinil compound. (Tr. 1740:23-1741:3, 1910:8-1911:1 (Aristoff) May 19, 2014.)

Accepting Dr. Buchwald's own definition²⁶ of stereoselective, for the reasons set forth below the Court concludes that the '814 patent does not disclose a “stereoselectively produced

²⁶ The Court notes that Dr. Aristoff also agrees with this definition and it supports his view of stereoselectively produced isomeric compound. (Tr. 1724:13-1725:12 (Aristoff), May 16, 2014; PTX-480 at Sandoz-Trep84014.)

isomeric compound” of treprostinil. (Tr. 1731:18-20 (Aristoff), May 16, 2014.)

i. Sandoz failed to prove the products of the '117 patent and the '814 patent are structurally and functionally the same

As the inventor of treprostinil, Dr. Aristoff had “no doubt” that there are structural differences between the '117 patent product and the '814 patent product. (Tr. 1758:7-10 (Aristoff) May 16, 2014.) As Dr. Aristoff illustrated to this Court on direct examination, the overall yield of the '814 patent is different than the overall yield of the '117 patent, in both the actual yield and the theoretical yield. The calculated yield of the stereoselectively produced treprostinil made by the '117 patent based on Example 1 is approximately 3%. Because the treprostinil product of the '117 patent is stereoselectively produced, the theoretical maximum yield of the '117 patent is 100% because each step is stereoselective. (Tr. 1741:20-24, 1744:8-18 (Aristoff), May 16, 2014.)

The disparity between the yields of the '117 patent process and the yields of the '814 patent process effectively prove that the structural and functional differences the two products are real and tangible. For example, the calculated yield of the '117 patent is approximately 10 to 30 times greater than the yield of the '814 patent, and the '117 patent has twice the theoretical yield making it structurally different. (Tr. 1741:19-24, 1742:24-1743:1, 1742:24-1743:16, 1757:21-25 (Aristoff), May 16, 2014; PTX-2; DTX-55; DTX-59 at UTC-Sand-Rem 61893-922.) Furthermore, because the final treprostinil product of the '814 patent resulted in a 1:1 mixture of diastereomers, only half of the product would be the targeted treprostinil structure—comprised of the targeted drug substance—so the product could be functionally different as well. (Tr. 1721:8-22, 1736:21-1738:8, 1756:23-1757:9 (Aristoff), May 16, 2014; DTX-56 at UTC-Sand-Rem 1096100.) Finally, as a practical matter, whereas the synthesis disclosed in the '814 patent resulted in a 1:1 mixture of diastereomers, which required throwing away at least half of the product, the '814 patent process was costly, wasteful, and inefficient—ultimately unsuitable for the production of treprostinil on a commercial scale.

Sandoz relies heavily on lots of treprostinil produced by Upjohn prior to the invention that led to the '117 patent—and internal documents describing those lots that were not available to the public as of the priority date of the '117 patent—to support their claim that the '814 patent is anticipatory prior art. (Tr. 1422:16-1423:13, 1441:5-17, 1443:7-1445:10, 1447:10-16, 1449:19-

1450:2, 1451:10-20, 1453:24-1454:14 (Buchwald), May 15, 2014; PTX-2 at 1; DTX-59; PTX-493; DTX-56; DTX-57; PTX-521; DTX-386; DTX-58.) UTC contends that Sandoz is not entitled to rely on the Upjohn lots as prior art on grounds that the information regarding those lots was not public before the priority date. In reply, Sandoz maintains that “UTC misunderstands the purpose of this evidence.” Def. Post-Trial Brief at p. 48. Sandoz argues that the “[t]he ‘814 patent, of course, was public” and that “[t]he Upjohn lots are simply embodiments of the ‘814 patent which show that the product of the ‘814 patent was the same as the product of the ‘117 patent.” *Id.* In this, both parties agree that the Upjohn lots are not prior art. As to any alternative evidentiary value to Sandoz, the Court finds that the disputed documents nevertheless work against Sandoz in that they prove that the prior Upjohn route used to make treprostinil had many significant problems—the mixture of diastereomers caused significant separation and scale-up problems among others—which coalesce to constitute a structurally different treprostinil product. (Tr. 1747:21-1748:18, 1762:15-1764:19 (Aristoff), May 16, 2014; DTX-171 at Sand-Trep 5997; PTX-493 at UTC-Sand-Rem176-177, 216.)

A person of ordinary skill in the art would recognize that for every organic synthesis there are small changes between each attempt resulting in small fluctuations in yield, impurities present, and other results. A person of ordinary skill in the art would also recognize that because of these fluctuations, comparing the average yield, purity and amounts of impurities generated in a synthesis is a standard practice. (Tr. 1459:18-1460:2 (Buchwald), May 15, 2014; Tr. 1753:8-1754:2 (Aristoff), May 16, 2014.) For lots of treprostinil made by both United Therapeutics and the Upjohn Company, confidential documents disclosing the impurity profiles of each lot showed the different relevant impurities characteristically present in each batch.²⁷ (Tr. 1750:25-1754:2 (Aristoff), May 16, 2014.) Whereas Sandoz performed a limited analysis of only seven lots to compare the treprostinil made by the Upjohn route to the treprostinil made by the ‘117 patent, (Tr. 1750:25-1751:24 (Aristoff), May 16, 2014.), the Court finds that Dr. Aristoff performed a more complete and fair analysis of over 57 lots including development and commercial lots of treprostinil made

²⁷ Possible treprostinil impurities present in lots made by United Therapeutics and the Upjohn company included 3 possible diastereomers of treprostinil designated as 1AU90, 2AU90, and 3AU90. Other structures identified as potential impurities of treprostinil include the intermediate benzindene triol designated as 97W86, the methoxy diol designated as 98W86, the ester dimer of treprostinil designated as 750W93, the 3-hydroxy ester dimer of treprostinil designated as 751W93 and the methyl ester and ethyl ester of treprostinil as well as others. (Tr. 1752:3-20, 1752:25-1753:5, 1753:18-1755:2 (Aristoff), May 16, 2014; PTX-521 at UTC-Sand-Rem21933-938, 21985; PTX-742 at UTC-Sand-Rem158436, 158438; PTX-753 at UTC-Sand-Rem334055-057; PTX-894 at UTC-Sand-Rem1104230-233; PTX-905 at UTC-Sand-Rem1156295-302.)

from 1997 to 2004 to determine whether the impurity profiles are different. (*Id.*) Dr. Aristoff further prepared a detailed chart of his analysis, which analyzed 5 different impurities for all of the lots, as well as the total related substances and batch size. (*Id.*; Tr. 1751:25-1752:10 (Aristoff), May 16, 2014; PTX-100a at 1-4, PTX-521 at UTC-Sand-Rem21933-938, 21985, PTX-742 at UTC-Sand-Rem158436, 158438, PTX-753 at UTC-Sand-Rem334055-057, PTX-894 at UTC-Sand-Rem1104230-233, PTX-905 at UTC-Sand-Rem1156295-302.) The results of that analysis reveal that:

- On average, prior Upjohn lots of treprostinil product that were made using the optimized route described in the Upjohn DMF are structurally different and less pure than treprostinil lots made by the '117 patent in which the Upjohn lots had approximately four times as much total impurities. (Tr.1755:3-16 (Aristoff), May 16, 2014; PTX-100a at 1-4.)
- On average, prior Upjohn lots of treprostinil product that were made using the non-public optimized route described in the Upjohn DMF are structurally different than treprostinil lots made by the '117 patent in which the Upjohn lots had approximately twenty times as much of the diastereomeric impurity 2AU90 than the average United Therapeutics lot. (Tr. 1754:3-11 (Aristoff), May 16, 2014; PTX-100a at 1-4.)
- On average, prior Upjohn lots of treprostinil product that were made using the Upjohn route are structurally different than treprostinil lots made by the '117 patent in which the Upjohn lots had approximately ten times as much of the dimer impurities 750W93 and 751W93 than the average United Therapeutics lot. (Tr. 1754:17-1755:2 (Aristoff), May 16, 2014; PTX-100a at 1-4.)
- One of the lots used in Dr. Aristoff's analysis was the Upjohn lot 15AU81WC ("the WC lot"). As described in the Upjohn DMF, the Upjohn lots required 5-10 recrystallizations. (Tr. 1902:6-12, 1903:2-13 (Aristoff), May 19, 2014; PTX-100a at 1; Tr. 2461:3-2462:6 (Moriarty), May 27, 2014; Tr. 1447:10-1448:24, 1449:5-7 (Buchwald), May 15, 2014; DTX-57 at UTC-Sand-Rem1161350.) With each recrystallization, material is lost, resulting in less and less product. (Tr. 1455:25-1456:4 (Buchwald) May 15, 2014.) The WC lot produced by the Upjohn route was smaller in scale than many of the United Therapeutics lots, yet still had more impurities. (Tr. 1890:15-18 (Aristoff), May 19, 2014; PTX-100a at 1-4.)

In light of the foregoing facts, the Court finds that the product of the '814 patent is structurally

different than the product created by the '117 patent in that the '117 patent pathway creates a distinct product with a superior impurity profile. (Tr. 1900:15-17 (Aristoff), May 19, 2014.)

Conclusion

Pursuant to same, the Court concludes that claim 1 of the '117 patent is not anticipated by any prior art reference. (Tr. 1758:1-10 (Aristoff), May 16, 2014.)

b) Dependent Claim 2

Claim 2 of the '117 patent is a dependent claim which depends from claim 1 and the only difference between claim 1 and claim 2 is that claim 2 specifies certain substituents for the structure of “the stereoselectively produced isomeric compound” directed to treprostinil. (Tr. 966:4-21 (Williams), May 13, 2014; PTX-2 at 22:38-41.) Accordingly, and for the reasons outlined above, claim 2 of the '117 patent is valid and not anticipated by any prior art reference.

c) Independent Claim 3

Claim 3 of the '117 patent claims a “stereoselectively produced isomeric compound according to the following formula”; it differs from claim 1 in that it then gives a single final chemical formula with no variables, providing “a drawing of the molecular structure of the treprostinil molecule.” (Tr. 967:6-20 (Williams), May 13, 2014; PTX-2 at 22:42-23:52.) Accordingly, and for the reasons outlined above, claim 3 of the '117 patent is valid and not anticipated by any prior art reference.

d) Independent Claim 4

The analysis outlined above for independent claim 1 is applicable to independent claim 4 as well in that the only significant difference between Claim 1 and Claim 4 of the '117 patent is that “the stereoselectively produced isomeric compound” of Claim 4 “is directed to pharmacologically acceptable salt forms of treprostinil,” including treprostinil sodium. (Tr. 1838:14-21 (Aristoff), May 19, 2014; PTX-2.) Accordingly, and for the reasons outlined above, claim 4 of the '117 patent is valid and not anticipated by any prior art reference.

Conclusion

In light of the foregoing facts and findings, the Court concludes that the '117 patent is not anticipated by any prior art reference.

Obviousness

In addition to its anticipation arguments, Sandoz also contends that the claims of the '117 patent are obvious. Sandoz contends that it would be obvious to take prior art treprostinil, which has a different impurity profile as compared to the product of the '117 patent, and “apply standard purification techniques” to arrive at the claimed treprostinil product. (Tr. 1465:6–15 (Buchwald), May 15, 2014 (explaining his obviousness opinions).)

UTC disputes Sandoz’s claims regarding “obvious” purification on the grounds of hindsight bias, and further contends that where the patent claims are directed to a “***stereoselectively produced*** isomeric compound,” “[p]urifying non-stereoselectively produced treprostinil to obtain a more pure product, likely at great cost in terms of product lost to purification, does not make the resulting product “stereoselectively produced.” Pl.’s Post-Trial Brief at 48. The Court agrees.

For the reasons set forth below, the Court concludes that Sandoz has failed to prove by clear and convincing evidence that the claims of the '117 patent are obvious over the prior art.

Differences Between the Claims and the Prior Art

(i) Independent Claim 1

A person of skill in the art would recognize that a process that produces a 1:1 mixture of diastereomers in the last seven steps of the synthesis is a significant problem and does not result in a stereoselectively produced product. (Tr. 1720:24-1721:5, 1739:3-11, 1740:20-23 (Aristoff), May 16, 2014.) For the '814 patent, over two-thirds of the material is lost in the last step. (Tr. 1761:4-20 (Aristoff), May 16, 2014.) Indeed, even for the optimized Upjohn route used to make the Upjohn lot 15AU81WC, the final step had a yield of 12%, which is very poor. The reference standard 15AU81WE obtained a purity of over 99%, but a person of ordinary skill would recognize the reference standard was taken from the WC lot and further purified for a total of 12 recrystallizations and a column chromatography. As Dr. Aristoff explained, the impurity profile still had 10 times the amount of the 2AU90 impurity over the average '117 patent product lot. (Tr. 1761:21-1762:9 (Aristoff), May 16, 2014.) At the time of the invention, known purification techniques such as chromatography and crystallization were already used as part of the disclosures of the '814 patent

so a person of ordinary skill in the art would not continue to redo these purification methods as it was not routine to do 5-10 recrystallizations. (Tr. 1762:10-14, 1764:4-10 (Aristoff), May 16, 2014; PTX-493 at UTC-Sand-Rem176-177, 216.)

As explained in detail above, the crux of the obviousness analysis is proof that a person of ordinary skill in the art "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994 (quoting *Pfizer*, 480 F.3d at 1361); see also *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009).

With respect to Defendant's obvious purification argument, Sandoz's own expert, Dr. Buchwald, conceded that performing 5-10 recrystallizations was "certainly not desirable and not common". (Tr. 1465:21-1466:2 (Buchwald), May 15, 2014.) Dr. Buchwald further testified that purification is unpredictable as "there's no guarantee of success when you do recrystallization" and the purifications used in the prior art for treprostinil could in fact make a compound more impure which happened with certain batches of treprostinil. (Tr. 1465:21-1466:2, 1466:3-8, 1466:12-22 (Buchwald), May 15, 2014.) Based on these concessions, the Court finds that Sandoz has failed to prove that it would have been obvious to a skilled artisan to purify the prior art treprostinil.

Nevertheless, UTC is correct in its assertion that even a finding of obvious purification would not render obvious the claimed invention. The '117 patent claims are directed to a "***stereoselectively produced*** isomeric compound," and the Court has construed "stereoselectively produced" to modify the compound, treprostinil. Purifying non-stereoselectively produced treprostinil may or may not yield a more pure product; but it does not make the resulting product "stereoselectively produced."

As the original inventor of treprostinil, Dr. Aristoff provided persuasive testimony in favor of nonobviousness: When prompted by the Court, Dr. Aristoff testified that prior to the invention of the '117 he and others tried to design a process that resulted in a stereoselective compound, and failed. (Tr. 1765:2-10 (Aristoff), May 16, 2014) ("I wanted to do a stereoselective procedure, I just couldn't come up with one.") Dr. Aristoff further testified that he was "impressed" with the '117 patent synthesis because it prepared all five chiral centers in a relatively few number of steps in good yield and admitted it was better than his synthesis. (Tr. 1720:3-16 (Aristoff), May 16, 2014.) Although aware of the Pauson-Khand reaction when he invented the '814 patent, Dr. Aristoff admitted that he did not consider using it to make treprostinil because he could not think of a way to

make the molecule stereoselective and did not think the reaction could be used on a commercial scale. (Tr. 1716:10-25, 1718:16-1719:23 (Aristoff), May 16, 2014; DTX-171.) Dr. Aristoff also explained that the Pauson-Khand is not commonly used in the pharmaceutical context, in fact, Dr. Aristoff did not know of any other commercial use of the Pauson-Khand reaction. (Tr. 1719:24-1720:2 (Aristoff), May 16, 2014.)

Significantly, Dr. Aristoff testified that UTC had considered the '814 patent in making treprostinil, but concluded that it was not stereoselective and that they could not scale it up and decided not to use it. Dr. Aristoff explained “[t]his prior work did not offer much guidance for our purification of the final product of UT-15 -- that’s treprostinil -- because they had a mixture of stereoisomers at this stage; the unacceptably lower recovery of the product was not relevant because in contrast to the Upjohn work, we have a pure stereomer at the stage of trial [sic] 66 and 1.” (Tr. 1762:19-1764:10 (Aristoff), May 16, 2014; PTX-493 at UTC-Sand-Rem176-177, 216.)

In light of Dr. Aristoff’s testimony, and the overwhelming evidence revealing the level of knowledge, work, and innovation required to reach the end result of the '117 patent—a stereoselective treprostinil product—at the time of the invention, the Court concludes that Claim 1 of the '117 patent is not obvious over the prior art.

(ii) Dependent Claim 2

Claim 2 of the '117 patent is a dependent claim which depends from claim 1 and the only difference between claim 1 and claim 2 is that claim 2 specifies certain substituents for the structure of “the stereoselectively produced isomeric compound” is directed to treprostinil. (Tr. 966:4-21 (Williams), May 13, 2014; PTX-2.) For the same reasons set forth above, claim 2 of the '117 patent is valid and is not obvious over the prior art for the same reasons as claim 1.

(iii) Independent Claim 3

Claim 3 of the '117 patent claims a “stereoselectively produced isomeric compound according to the following formula”; it differs from claim 1 in that it then gives a single formula with no variables, providing “a drawing of the molecular structure of the treprostinil molecule” as the final product compound. (Tr. 967:6-20 (Williams), May 13, 2014.) For the same reasons set forth above, claim 3 of the '117 patent is valid and not obvious over the prior art for the same reasons as claim 1.

(iv) *Independent Claim 4*

Claim 4 of the '117 patent "is directed to pharmacologically acceptable salt forms of treprostinil," including treprostinil sodium. (Tr. 1838:14-21 (Aristoff), May 19, 2014; PTX-2.) For the same reasons set forth above, claim 4 of the '117 patent is valid and not obvious over the prior art.

Objective Considerations of Non-Obviousness

As previously indicated, secondary considerations must also be considered by this Court. Again, Dr. Aristoff persuasively testified, as follows, that such secondary considerations, namely failure of others; long-felt need, unexpected results, and commercial success, weigh heavily in favor of nonobviousness:

Failure of Others and Long-felt Need

As Drs. Aristoff, Moriarty, Rothblatt, and Williams testified, at the time of the invention of the '117 patent, there was a long-felt need to have a better treprostinil product in a stereoselective form made in a cost-effective manner. (Tr. 217:14-221:5 (Rothblatt), May 2, 2014 (testifying prior method "was so impractical, it had been a method developed by Upjohn...this method was so impractical, it created one kilogram of toxic waste for every gram of this medicine that was made" and that she instructed her staff "find me somebody who can make this...And they fanned out across the country; they talked to more than a hundred different chemists, mostly at universities, and everybody said no."); Tr. 1765:2-10 (Aristoff), May 16, 2014 (testifying that he "wanted to do a stereoselective procedure, [he] just couldn't come up with one").) Early efforts in synthesizing treprostinil suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences. (Tr. 1745:3-21 (Aristoff), May 16, 2014.) That lack of stereocontrol meant that substantial amounts of stereoisomers of treprostinil had to be carried through the synthesis process only to be purified and discarded at or close to the final stages. This led to long synthetic pathways, materially lower yields and, as a result significantly higher costs to produce acceptable amounts of the drug. (Tr. 1761:5-20 (Aristoff), May 16, 2014.) Even though prior methods for the synthesis of treprostinil were known, no one had successfully commercialized treprostinil until the invention of the '117 patent.

As the creator of treprostinil, Dr. Aristoff admitted that he and others tried to design a process that resulted in a stereoselective compound, and failed. (Tr. 1765:2–10 (Aristoff), May 16, 2014) (“I wanted to do a stereoselective procedure, I just couldn’t come up with one.”.) *See also Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003) (“[T]here can be little better evidence negating an expectation of success than actual reports of failure.”).

Unexpected Results

Prior to the ’117 invention, persons of ordinary skill in the art had also failed to arrive at its synthetic approach to treprostinil. (Tr. 1974:4-12 (Williams), May 22, 2014; PTX-493 at UTC-Sand-Rem00000216.) Because the Pauson-Khand reaction was known to be unpredictable, scientists were seemingly reluctant to experiment with it in this context. (Tr. 1977:8-13, 1977:22-1978:14 (Williams), May 22, 2014; PTX-574 at UTC-Sand-Rem00070025.)

When, for example, United Therapeutics retained Dr. Robert M. Moriarty and his team of chemists at Steroids LTD (later Synquest, Inc.) in Chicago, Illinois to develop a commercially viable synthesis for stereoselectively produced treprostinil, Dr. Moriarty and Steroids LTD identified and investigated several different potential theoretical synthesis routes that might be viable and were worth investigating. (Tr. 219:1-220:22 (Rothblatt), May 2, 2014; Tr. 2444:8-16 (Moriarty), May 27, 2014.) Of those, the Pauson-Khand reaction was not the most promising of those routes due to the unpredictability of the reaction. (Tr. 2441:20-2442:3, Tr. 2445:19-2446:15 (Moriarty), May 27, 2014; Tr. 2420:23-2421:7 (Rao), May 27, 2013; Tr. 1977:8-13, 1977:22-1978:14 (Williams), May 22, 2014; PTX-574 at UTC-Sand-Rem00070025.) Furthermore, the literature teaching the synthetic routes to benzindene prostacyclin analogs and other pharmaceutical substances did not include the use of the Pauson-Khand reaction, and thus taught away from the ’117 invention’s use of the Pauson-Khand reaction for synthesizing prostacyclin analogs because it had never been used for that purpose. (Tr. 1719:24-1720:2, 1732:10-11 (Aristoff), May 16, 2014.)

In an even more illustrative example, as the inventor of treprostinil, Dr. Aristoff testified that he did not even think of using the Pauson-Khand reaction to synthesize a stereoselectively produced treprostinil product and was surprised that it worked as well as it did. (Tr. 1719:15-23, 1720:5-16 (Aristoff), May 16, 2014.) Dr. Aristoff admitted that he had tried to optimize and improve the treprostinil product made by the ’814 patent, but could not overcome the problems with the

mixtures of diastereomers and other impurities and was ultimately unsuccessful. As Dr. Aristoff and others testified, the success of the Pauson-Khand reaction in producing stereoselective treprostinil was therefore unexpected.

Commercial Success

Finally, as previously noted, Remodulin is undisputedly a commercial success that has had a tremendous impact on United Therapeutics' total revenues, revenue growth, financial performance, and market capitalization. (Tr. 227:14-228:17 (Rothblatt), May 2, 2014; Tr. 1922:18-1923:16 (Gering), May 19, 2014; PTX-113; PTX-692.) (Tr. 1915:14-1916:24, 1923:17-1925:19, 1927:6-1930:16 (Gering), May 19, 2014; Tr. 1321:12-15 (Vander Veen), May 14, 2014; PTX-111; PTX-112; PTX-113; PTX-114; DTX-459 at UTC-Sand- Rem01096012; PTX-971; DTX-129.)

Remodulin has generated significant sales and sustained sales growth, with sales steadily climbing from \$21.2 million in 2002 to \$66 million in 2004 and to \$458 million in 2012. (Tr. 1918:8-24 (Gering), May 19, 2014; Tr. 1322:25-1323:2 (Vander Veen), May 14, 2014; PTX-111; PTX-113.) Since its launch in 2002, cumulative sales for Remodulin are approximately \$3 billion through December 31, 2013. (Tr. 1918:8-24 (Gering), May 19, 2014; Tr. 1322:9-14 (Vander Veen), May 14, 2014; PTX-111; PTX-113.) Remodulin has had revenue growth in every year from 2002 to 2012. (Tr. 1918:8-24 (Gering), May 19, 2014; PTX-111; PTX-113.) The average annual percentage growth of Remodulin revenue is 39 percent. (Tr. 1918:8-24 (Gering), May 19, 2014; Tr. 1322:15-19 (Vander Veen), May 14, 2014; PTX-111.)

The profit margins of Remodulin are consistent with commercial success: UTC as a company had an average operating profit of approximately 31 percent between 2009 and 2012 and Dr. Rothblatt testified that the profit margin on Remodulin was approximately 90 percent. (Tr. 1918:8-24 (Gering), May 19, 2014; Tr. 232:3-4 (Rothblatt), May 2, 2014; PTX-113.) Remodulin has captured and maintained a significant portion of the overall PAH market as well as subsections of that market. (Tr. 1918:25-1919:23 (Gering) May 19, 2014; PTX-114.) Remodulin represents over 70 percent of the parenteral prostacyclin market, including generics, (Tr. 1921:7-14 (Gering), May 19, 2014; PTX-112.), and Remodulin is the only prostacyclin in the U.S. market that can be administered through subcutaneous infusion, which has certain advantages over intravenous infusion. (Tr. 315:5-317:3 (White), May 7, 2014.)

The treprostinil syntheses used prior to the '117 patent were considered impractical for

large-scale preparation. (Tr. 1923:17-1925:19 (Gering), May 19, 2014; Tr. 1981:14-1982:10 (Williams), May 22, 2014; DTX-171 at Sandoz-Trep 0005997-8; PTX-459 at UTC-Sand-Rem01096012.) Thus, as several witnesses testified, they were not were not commercially feasible. (Tr. 1975:20-1976:6 (Williams), May 22, 2014; Tr. 1923:17-1925:19 (Gering), May 19, 2014; PTX-493 at UTC-Sand-Rem00000216; Tr. 2442:24-2443:17 (Moriarty), May 27, 2014; Tr. 218:2-221:5 (Rothblatt), May 2, 2014; Tr. 1720:9-18 (Aristoff), May 16, 2014.) Without the claimed features of the '117 patent, Remodulin would not be commercially viable. (Tr. 1982:11-13 (Williams), May 22, 2014; Tr. 1923:17-1925:19 (Gering), May 19, 2014; PTX-459 at UTC-Sand-Rem01096012; Tr.1975:20-1976:6 (Williams), May 22, 2014; PTX-493 at UTC-Sand-Rem00000216; Tr. 2442:24-2443:17 (Moriarty), May 27, 2014; Tr. 218:2-221:5 (Rothblatt), May 2, 2014; Tr. 1720:9-18 (Aristoff), May 16, 2014.) Indeed it is the '117 patent that enabled the production of Remodulin on a commercial scale, therefore enabling its commercial success. (Tr. 1982:14-1983:1 (Williams), May 22, 2014; Tr.1923:17-1925:19 (Gering), May 19, 2014; PTX-459 at UTC-Sand-Rem01096012; Tr. 2442:24-2443:17 (Moriarty), May 27, 2014; Tr. 218:2-221:5 (Rothblatt), May 2, 2014; Tr. 1720:9-18 (Aristoff), May 16, 2014.) Accordingly, the '117 invention has a direct nexus to the commercial success of Remodulin. (Tr. 1923:17-1925:19 (Gering), May 19, 2014; Tr. 1981:5-10 (Williams), May 22, 2014.)

In light of the foregoing facts, the Court finds that objective indicia of obviousness weigh heavily in favor of nonobviousness. Accordingly, the Court concludes that Sandoz has failed to prove that the '117 patent is obvious over the prior art. Whereas, Sandoz has also failed to prove that the '117 patent is anticipated by the prior art reference, the Court concludes that the '117 patent is valid.

CONCLUSION

After careful consideration of the entire record in this case in light of the applicable law, the Court hereby concludes that: (1) UTC has failed to prove by a preponderance of the evidence that Sandoz's proposed ANDA product will induce infringement of the asserted claims of the '007 patent; (2) Sandoz has failed to prove by clear and convincing evidence that the asserted claims of the '007 are invalid; (3) UTC has proved by a preponderance of the evidence that Sandoz's ANDA product will infringe and induce infringement of the asserted claims of the '117 patent; and (4) Sandoz has failed to prove by clear and convincing evidence that the asserted claims of the '117

patent are invalid.

An appropriate order shall follow.

s/ Peter G. Sheridan

Hon. Peter G. Sheridan, U.S.D.J